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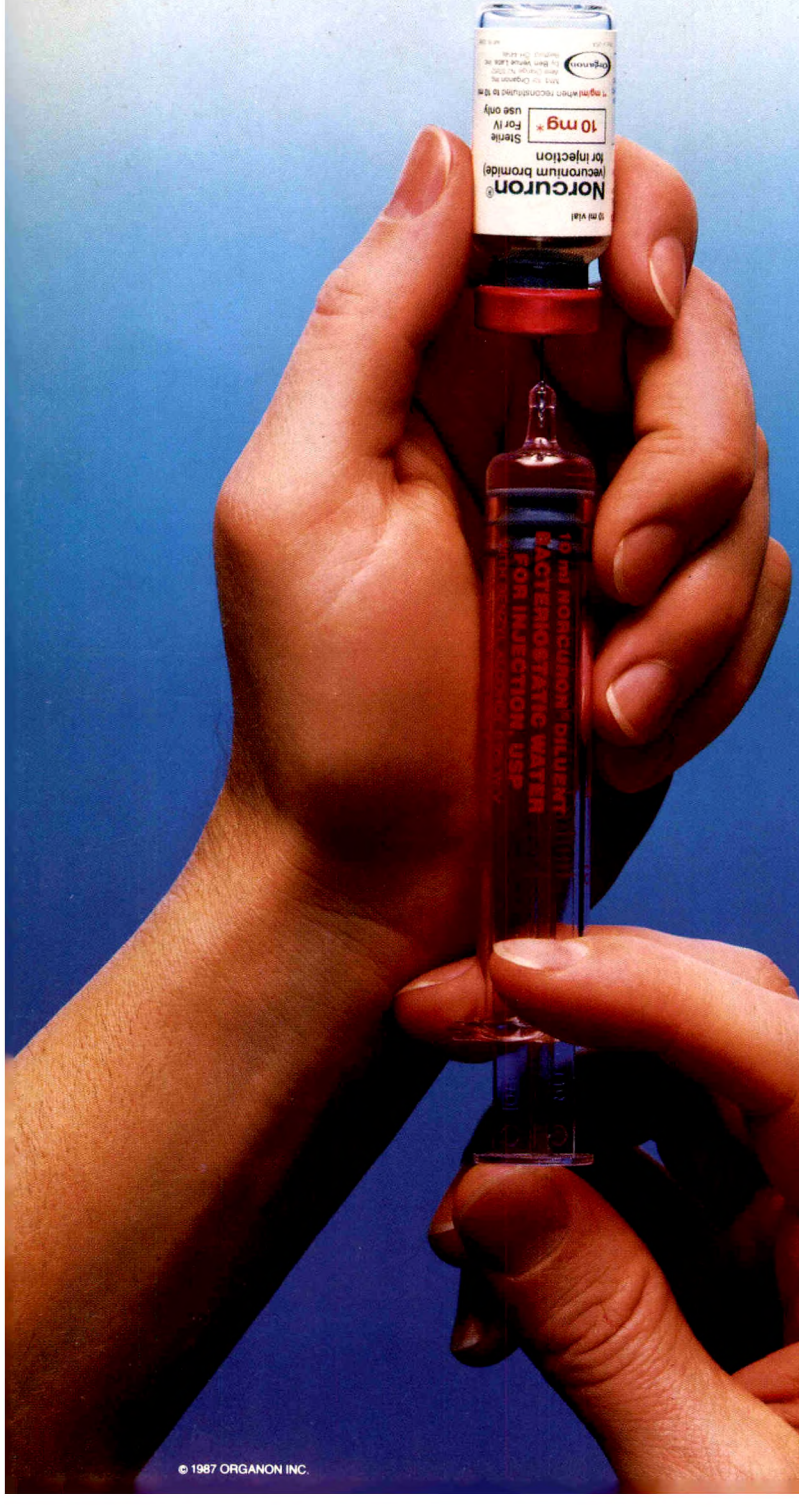

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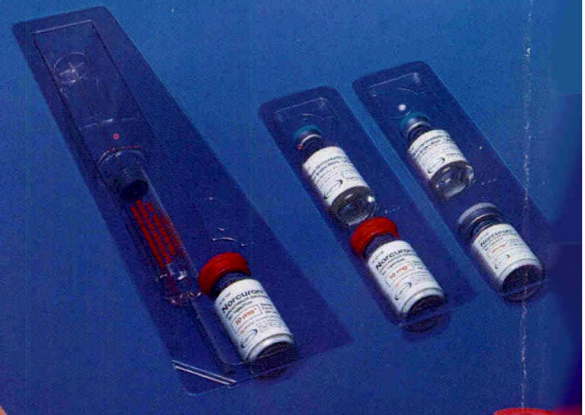

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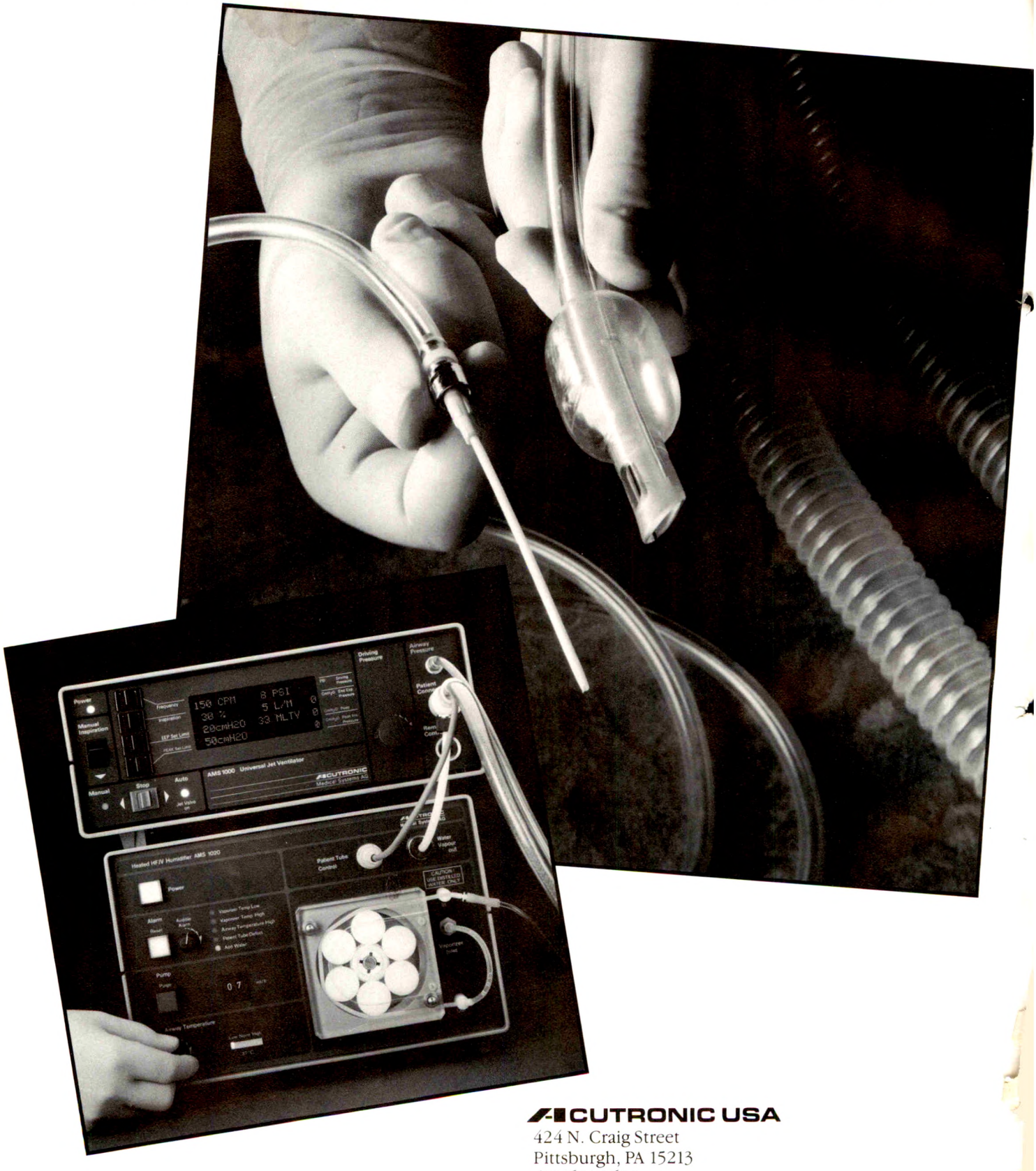

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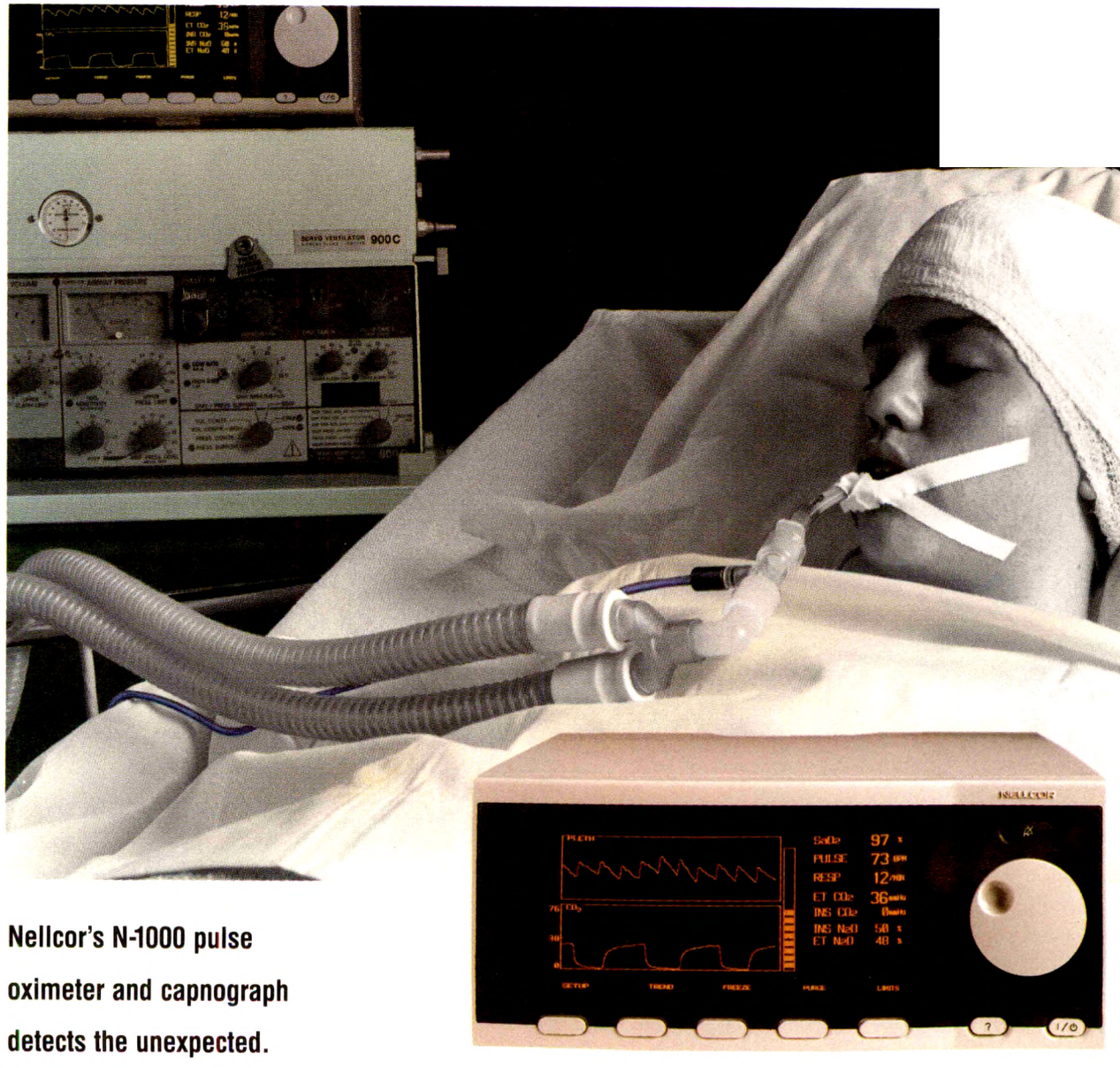

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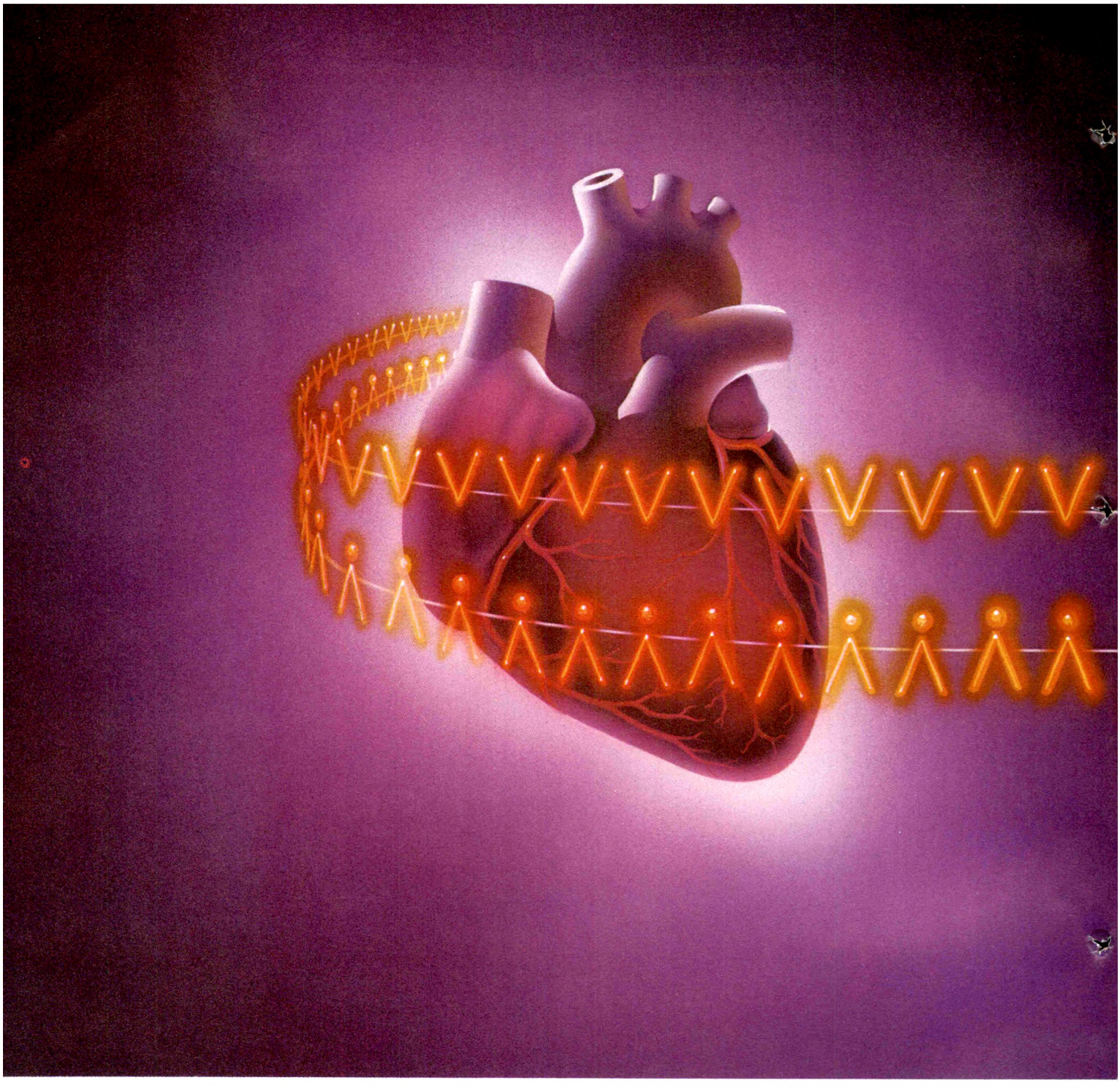

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Editorial

Interpleural Regional Analgesia

Benjamin G. Covino, PhD, MD

Key Words: ANESTHETIC TECHNIQUES—interpleural catheter technique. ANESTHETICS, LOCAL—bupivacaine. PAIN—postoperative.

A preliminary report of the analgesic activity of local anesthetics deposited into the pleural cavity was published in 1986 by two Norwegian anesthesiologists, Reiestad and Strömskag (1). These investigators described the results obtained with this technique in 81 patients in whom the following surgical procedures were performed: cholecystectomy with a subcostal approach, unilateral breast operations, and renal surgery. A single 20-ml dose of 0.5% bupivacaine with epinephrine was reported to produce complete analgesia in 78 of the 81 patients with a mean duration of 10 hours. The relative ease of performing this procedure and the apparently high frequency of adequate postoperative analgesia with minimal adverse effects have captured the interest of a number of investigators interested in the field of postoperative analgesia. In less than 2 years, a number of articles on this topic have been published (2–8), and four abstracts on this subject have been accepted for presentation at the 1988 Meeting of the International Anesthesia Research Society.

As with any new anesthetic procedure, a number of questions remain to be answered. One controversy that should be immediately resolved concerns the appropriate nomenclature regarding this technique. The original article by Reiestad and Strömskag was entitled "Interpleural Catheter in the Management of Postoperative Pain." Subsequent articles have used the word "intrapleural." In the current issue of this Journal, the article by Strömskag et al. (8) employs the word "intrapleural," whereas the case report by Durrani et al. (7) utilizes the word "interpleural." The technique involves the percutaneous introduction of a catheter into the thoracic cage between the parietal and visceral pleura. Therefore, the term "interpleural regional analgesia" would appear more appropriate because the catheter is located and the local anesthetic solution deposited between the two layers of pleura rather than within the pleura. One could argue that the anesthetic solution is injected within the pleural space and thus the term "intrapleural" is appropriate. However, if the technique is referable to the pleural space, which can be considered analogous to the epidural space because both are only potential spaces, then the prefix "intra" is unnecessary. It is hoped that future articles concerning this analgesic procedure will employ a common terminology based on anatomic considerations; interpleural would appear to be the most appropriate adjective to describe this technique.

What is the mechanism of analgesia produced by this technique? It has been suggested that the local anesthetic solution diffuses from the pleural space through the parietal pleura and the innermost intercostal muscle to reach the intercostal space where blockade of the intercostal nerves occurs. Therefore, this technique should be analogous to the blockade of multiple intercostal nerves unilaterally. Differences appear to exist between the conventional form of intercostal nerve block and the interpleural technique. Intercostal nerve blocks are capable of providing a surgical level of anesthesia. The interpleural technique provides analgesia but not anesthesia sufficient for the performance of surgery. These differences in the degree of analgesia may be qualitative rather than quantitative. The administration of greater quantities of local anesthetic into the pleural space may result in a more profound depth of intercostal nerve blockade.

Is the intrathoracic sympathetic chain involved in the analgesia produced by this technique? If, indeed,

Received from the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

local anesthetics diffuse readily through the parietal pleura and intercostal muscles to block intercostal nerves, then the sympathetic chain that is separated from the pleural cavity only by the parietal pleura is also a potential site of action. The phrenic and splanchnic nerves may also be affected by local anesthetics deposited in the pleural space. The case report by Durrani et al. describing a remarkable degree of analgesia in a patient with severe pain due to carcinoma of the pancreas is suggestive of splanchnic nerve blockade (7).

A number of practical questions remain unanswered. What is the optimal local anesthetic dosage? Most authors have employed 20 ml of 0.5% bupivacaine. The current study by Strömskag et al. (8) suggests little difference in the analgesic activity of 20 ml of 0.25, 0.375, and 0.5% bupivacaine. A somewhat longer duration of analgesia was obtained with the 0.5% solution, but no statistically significant difference was observed between the various concentrations of bupivacaine. Is 20 ml the optimal volume to be employed? In the patient described by Durrani et al. (7), only 8 ml of 0.5% bupivacaine was required for complete pain relief. Controversy already exists concerning the appropriate volume of solution. One report suggests no difference in efficacy between 10 and 20 ml of 0.5% bupivacaine, whereas another study indicates that 30 ml of 0.5% bupivacaine was required for uniformly successful blocks (5,6). Clearly, more studies are required to determine the optimal volume, concentration, and total dosage of local anesthetic required for this technique. Moreover, the local anesthetic dosage requirement may differ depending on the etiology and location of the pain.

Should local anesthetic solutions with epinephrine be employed? Most studies have employed bupivacaine solutions containing epinephrine. However, the effect of epinephrine on the anesthetic activity and blood levels of bupivacaine have not been carefully investigated. Is bupivacaine the most appropriate anesthetic to be employed for this technique? Would agents such as lidocaine, mepivacaine, or etidocaine be equally effective and potentially less toxic than bupivacaine?

The technique currently described is useful only for the treatment of unilateral type of pain. Is this technique useful for patients in whom a transverse upper abdominal incision has been made or in whom the sternum has been split for thoracic or cardiac surgical procedures? Can one safely and effectively employ bilateral interpleural catheters for such situations? One of the papers to be presented at this year's International Anesthesia Research Society Meeting (not presently available) is concerned with the use of a bilateral interpleural procedure.

What is the distribution of the local anesthetic solution injected into the pleural space? Does all of the solution diffuse across the parietal pleura into the intercostal space? Does any of the solution cross the diaphragm into the peritoneal cavity? If local anesthetics are taken up by the diaphragm, does this influence respiratory function? Does diffusion across the visceral pleura occur into the substance of the lung? Perhaps, more important, does diffusion across the pericardial pleura and pericardium occur resulting in a possible direct topical effect on the myocardium? Pulmonary function studies have indicated that a significant increase in forced vital capacity and forced expiratory volume occurred after the administration of bupivacaine into the pleural cavity (5). The analgesia-related enhancement of respiratory effort probably outweighs any adverse effect of the unilateral phrenic nerve blockade and diaphragmatic depression that may be caused by the local anesthetic.

What are the potential adverse effects of this technique? The most obvious concern is the possible production of a pneumothorax. Although minor signs of pneumothorax have been observed in a few patients, to date this does not appear to be a clinically significant problem. Is the vascular absorption sufficiently rapid to produce potentially toxic anesthetic blood levels? An average arterial plasma concentration of 1.2 μg/ml bupivacaine has been observed after the interpleural administration of 100 mg bupivacaine with epinephrine (8). Others have reported mean peak venous plasma levels of approximately 2 μg/ml bupivacaine after the interpleural administration of 150 mg of this agent with epinephrine. It would appear that 100–150 mg of bupivacaine should not result in toxic blood levels. It is not certain whether the relatively low blood levels are related to the use of epinephrine-containing solutions. Central nervous system toxicity has occurred in one patient in whom a venous plasma level of approximately 5 μg/ml bupivacaine was reported (3). This patient had a recent history of pneumonia, which may have resulted in a rapid absorption of the local anesthetic. Little is known at present concerning the use of this technique in patients with various pathologic pulmonary states. It was originally reported that adequate analgesia was not obtained in a patient with pulmonary fibrosis due to tuberculosis (1). On the other hand, this technique was successfully employed in two patients with cystic fibrosis (4).

In summary, the administration of local anesthetic solutions into the pleural cavity by means of an interpleural catheter represents a new and unique

form of regional analgesia that has proven advantageous for postcholecystectomy pain with a subcostal incision, unilateral breast operations, renal surgery, multiple rib fractures, and pancreatic pain. The usefulness for postthoracotomy pain is still somewhat uncertain. As with any new procedure, a number of questions remain, including the mechanism of action, the appropriate local anesthetic solution to be employed and, most importantly, the benefit/risk ratio associated with this technique.

Well-designed scientific studies are required to define the ultimate usefulness and potential problems associated with this new procedure. Until more information becomes available, this technique should be employed with appropriate precautions and with the fully informed consent of the patient.

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Intrapleural Administration of 0.25%, 0.375%, and 0.5% Bupivacaine with Epinephrine after Cholecystectomy

Kjell Erik Strömskag, MD, Finn Reiestad, MD, Ewa L. O. Holmqvist, CRNA, and Stephan Ogenstad, PhD

STRÖMSKAG KE, REIESTAD F, HOLMQVIST ELO, OGENSTAD S. Intrapleural administration of 0.25%, 0.375%, and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 1988;67:430–4.

Thirty patients who had undergone cholecystectomy (subcostal incision) were randomly allocated to three groups of ten patients each and given intrapleural injections of 20 ml 0.25% (group I), 0.375% (group II), or 0.5% (group III) bupivacaine each with added epinephrine (5 μg/ml). Complete pain relief was obtained within 30 minutes in all but one patient in groups I and II. Pain scores (VAS, 0–100 mm) were recorded at regular intervals and did not exceed 20 mm (mean) in any group from 30 minutes up to 4 hours. Median time interval from the intrapleural injection to administration of supplementary analgesics was 4 hours 20 minutes, 6 hours, and 7 hours 45 minutes in groups I, II, and III, respectively. The maximum plasma concentration of bupivacaine (C_{max}), 0.62 (± 0.25 SD) μg/ml in group I, 0.82 (± 0.40) μg/ml in group II, and 1.20 (± 0.44) μg/ml in group III, was significantly higher in group III than in the other groups. The time to achieve maximum plasma concentration of bupivacaine (T_{max}) was approximately 15 minutes in all groups. No side effects were observed.

Key Words: ANESTHETIC TECHNIQUES—interpleural catheter technique. ANESTHETICS, LOCAL—bupivacaine. PAIN—postoperative.

Inadequate pain relief after upper abdominal surgery increases the incidence of pulmonary complications due to difficulty in coughing and taking deep breaths. Pain relief provided by opioids given intramuscularly or intravenously is associated with side effects, respiratory depression being the most serious (1). Particularly after subcostal incision, intermittent or continuous intercostal nerve block provides effective pain relief, although supplementary analgesics may be required (2,3). Epidurally administered morphine also gives effective postoperative pain relief, although the duration of analgesia is unpredictable and late respiratory depression has been reported (4,5).

Intrapleural administration of bupivacaine after upper abdominal surgery and in patients with multiple rib fractures provides satisfactory analgesia of long duration (6,7). However, when the present study was initiated, there were no data available on systemic uptake of bupivacaine after intrapleural injection.

The objectives of the present study were to determine the plasma levels and the analgesic effects of three concentrations of bupivacaine with added epinephrine after intrapleural administration to patients after cholecystectomy.

Materials and Methods

Thirty patients who had undergone cholecystectomy (subcostal incision) took part in this open study. The patients were classified randomly into three groups (ten patients in each group) and were given intrapleural injections of 20 ml 0.25% (50 mg, group I), 0.375% (75 mg, group II), or 0.5% (100 mg, group III) bupivacaine with added epinephrine (5 μg/ml).

Consent was obtained, and the investigation was performed in accordance with the recommendation of the Helsinki Declaration and was approved by the Norwegian Board of Health and Welfare. Patients with a history of traumatic or spontaneous pneumothorax, hemothorax, pleuritis, or allergy to local anesthetics were excluded from the study.

Received from the Department of Anesthesia, Molde County Hospital, Norway, the Pain Control, Clinical Research, and Department of Biostatistics, Astra, Sweden. Accepted for publication December 18, 1987.

Address correspondence to Dr. Strömskag, Department of Anesthesia, Molde County Hospital, N-6400 Molde, Norway.

Table 1. "Prince Henry" Pain Scale*

Definition	Score
No pain on coughing	0
Pain on coughing but not on deep breathing	1
Pain on deep breathing but not at rest	2
Pain at rest, slight	3
Pain at rest, severe	4

*From Ref. 8.

For premedication oxazepam (25–50 mg) was given orally approximately 1 hour before anesthesia. Surgery was performed under general anesthesia with thiopental, fentanyl, pancuronium, and nitrous oxide/oxygen.

After completion of surgery but before extubation, the patient was turned to the left side and an epidural catheter (Portex 16-gauge, closed end with three lateral eyes) was introduced 5–6 cm into the right pleural space through a 16-gauge Tuohy needle inserted at the eighth or ninth intercostal space, just above the upper edge of the lower rib, approximately 10 cm from the midline (6,7). General anesthesia was then discontinued and residual fentanyl effects were antagonized with 0.4 mg naloxone. When the patients reported pain after surgery, 20 ml of bupivacaine solution was injected according to randomization (following negative aspiration) intrapleurally. Injection time was 30–60 seconds.

The degree of postoperative pain was assessed using 1) a visual analogue scale (VAS, 0–100 mm) and, 2) a verbal rating scale, "Prince Henry" pain scale (8) (Table 1). Assessments were made when the patient first complained of pain after surgery and 5, 10, 15, and 30 minutes and 1, 2, 3, and 4 hours after injection. Patients who required supplementary analgesics were excluded from further assessments. The onset of complete analgesia was defined as the time from the intrapleural injection until the patient required further analgesics.

Systolic and diastolic blood pressures and heart rate were recorded before injection and at 5, 10, 15, 20, and 30 minutes after injection and then every 30 minutes up to 4 hours.

Radial arterial blood samples were taken at 5, 10, 20, 30, 60, 90, 120, 150, 180, and 240 minutes after the intrapleural injection. After centrifugation the plasma was separated and kept deep frozen (−20°C) until analysis by gas chromatography with nitrogen-selective detection. Assay sensitivity was 10 ng/ml with a coefficient of variation of 10%.

The pain assessment (VAS) was evaluated by repeated measures analysis. Differences in onset and duration of analgesia and T_{max} were analyzed by the Kruskal–Wallis one-way analysis of variance by ranks. Differences in C_{max} were analyzed by the Newman–Keuls multiple range test (9). $P < 0.05$ indicated a statistical significance. The results are expressed as the median or the mean (± SD) followed by the range of data.

Table 2. Patient Characteristics

	Group I (0.25% bupivacaine)	Group II (0.375% bupivacaine)	Group III (0.5% bupivacaine)
Age	50 ± 17.4*	53 ± 19.3	54 ± 19.7
Weight (kg)	73 ± 10.4	72 ± 21.1	68 ± 13.0
Height (cm)	171 ± 7.0	172 ± 15.0	165 ± 4.8
Sex	4M /6F	6M /3F	0M /10F

* Mean ± SD.

Results

The patients in the groups were similar with regard to age, weight, and height, although all patients in group III were women (Table 2). One patient in group II was excluded from the study as the intrapleural catheter was inserted on the morning after surgery.

Complete pain relief was obtained within 15–30 minutes in nearly all patients. Failure to obtain complete pain relief within 30 minutes was recorded in one patient in each of groups I and II. They required further analgesics and the pain scores for the patients were then excluded from analysis.

VAS showed a rapid decrease in pain in all groups during the first 30 minutes after injection. The mean score did not exceed 20 mm in any group from 30 minutes up to 4 hours (Fig. 1). No statistically significant differences were found between the groups.

The median duration of analgesia in group I was 4 hours 20 minutes (2 hours 5 minutes–16 hours), in group II, 6 hours (3 hours, 25 minutes–9 hours), and in group III, 7 hours 45 minutes (3 hours 20 minutes–18 hours) (Fig. 2). The differences were not statistically significant. Another six patients (three in group I, one in group II, and two in group III) required further analgesics (20 ml of the 0.5% solution) during the first 4 hours after injection. Accordingly, these patients were excluded from further assessments after the second injection.

Mean C_{max} values were 0.62 (± 0.25), 0.82 (± 0.40), and 1.20 (0.44) μg/ml in groups I, II, and III, respectively. C_{max} was significantly higher in group III than in the other groups. Mean T_{max} values were approximately 15 minutes in all groups (Table 3, Fig. 3).

Heart rate and systolic and diastolic blood pressures recorded before the intrapleural injection (after termination of general anesthesia) were similar in the

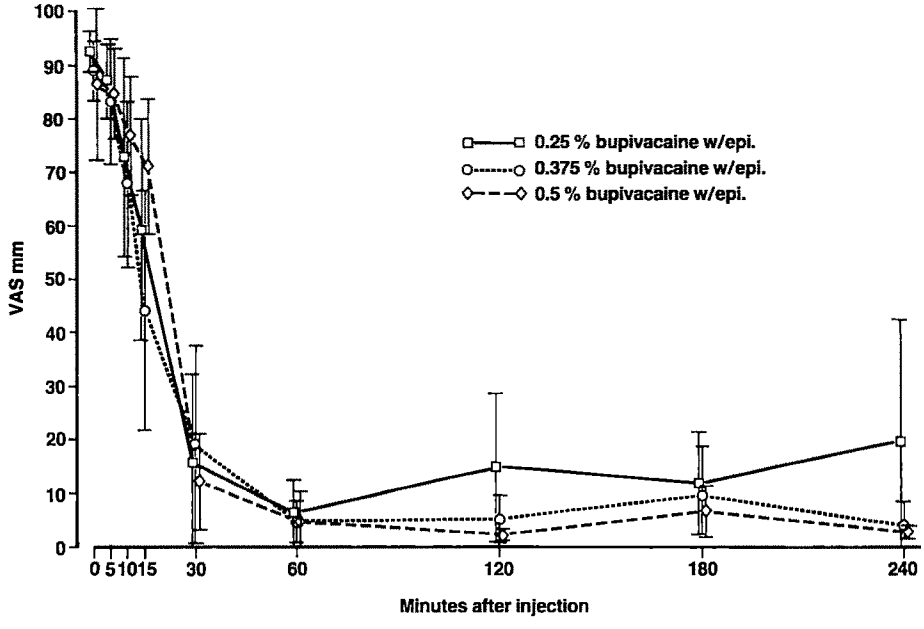

Figure 1. Relief of pain (VAS, 0–100 mm) at different time intervals after intrapleurally administered bupivacaine with epinephrine 5 μg/ml in doses of 50, 75, and 100 mg. Mean values and a 95% confidence level.

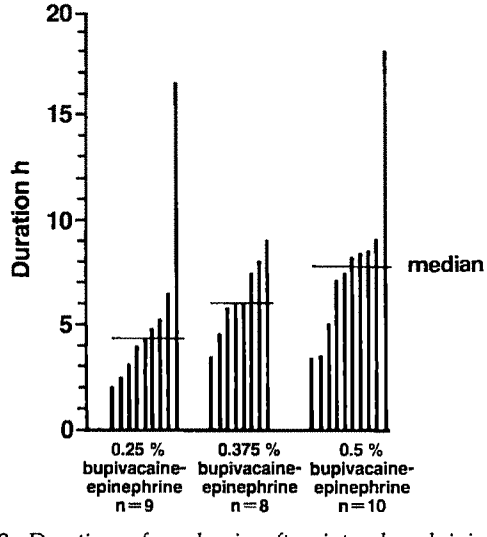

Figure 2. Duration of analgesia after intrapleural injection of 0.25% (50 mg), 0.375% (75 mg), and 0.5% (100 mg) bupivacaine with epinephrine 5 μg/ml. Individual and median values.

groups. During the first 30 minutes after injection, heart rate decreased 14% (± 11.5) in group I, 19% (± 12.9) in group II, and 23% (± 9.2) in group III. During the same time interval, the decrease in systolic blood pressures averaged 8 (± 14.1), 6 (± 11.1), and 11% (± 8.7) in groups I, II, and III, respectively. The corresponding decreases in diastolic blood pressure were 19 (± 12.8), 22 (± 13.6), and 27% (± 9.8) in the respective groups. No significant differences were found between the groups. Chest x-rays on the first postoperative day did not show pneumothorax in any patient.

Table 3. Arterial Plasma Concentrations of Bupivacaine after Intrapleural Injection using 20 ml 0.25%, 0.375%, and 0.5% Bupivacaine with 5 μg/ml Epinephrine

	Group I 0.25% bupivacaine (50 mg)	Group II 0.375% bupivacaine (75 mg)	Group III 0.5% bupivacaine (100 mg)
C_{max} (μg/ml)	0.62 ± 0.25* (0.33–1.22)	0.82 ± 0.40 (0.37–1.68)	1.20 ± 0.44†,‡ (0.39–1.80)
t_{max} (min)	15.0 ± 5.3 (10–20)	15.6 ± 8.8 (10–30)	17.0 ± 4.8 (10–20)

* Mean ± SD. The range is given in parentheses.
† Significant difference ($P < 0.01$) between groups I and III.
‡ Significant difference ($P < 0.05$) between groups II and III.

Discussion

Several methods are used to provide pain relief after thoracic and upper abdominal surgery. Despite side effects, including nausea, vomiting, and respiratory depression, the systemic use of opioids remains to be the most commonly used method (1,10). However, epidural administration of local anesthetic or opioids and intercostal block are also used, though less frequently (11,12).

In comparison with traditional intercostal block, the present method appears technically simpler for the anesthesiologist and less inconvenient for the patient. Only a single needle puncture is required, which may reduce the risk of pneumothorax, bleeding, or intravascular injection. Onset time and duration of analgesia appear to be comparable in both techniques (13). The intrapleural technique is also suitable for continuous infusion (7). In contrast to continuous intercostal block (2,3), intrapleural ad-

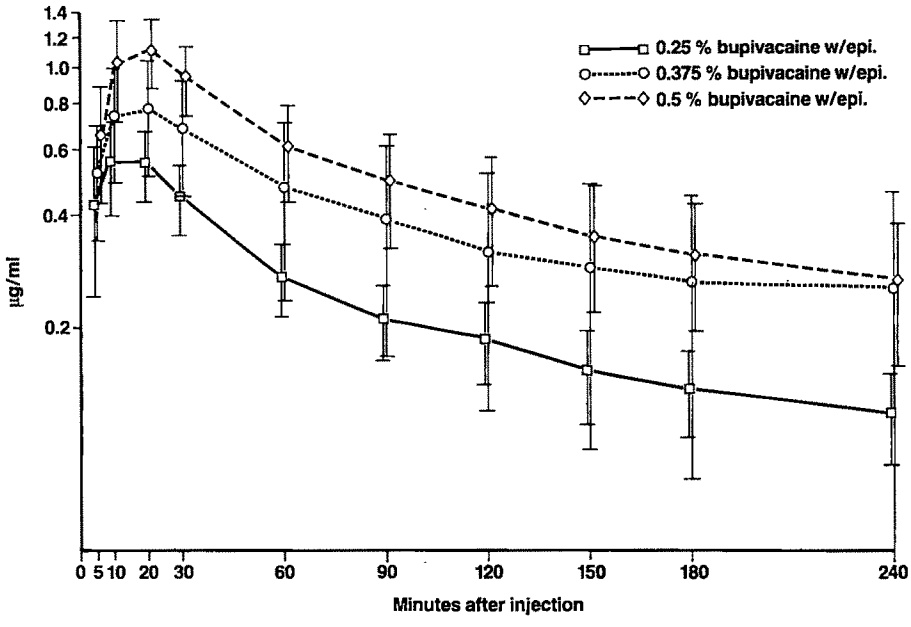

Figure 3. Arterial plasma concentrations at different time intervals after intrapleural injection of 0.25 (50 mg), 0.375% (75 mg), and 0.5% (100 mg) bupivacaine with epinephrine 5 µg/ml. Mean values and a 95% confidence level.

ministration of local anesthetics blocks almost all the intercostal nerves on the affected side (7).

In this study, the administration of 100 mg bupivacaine resulted in a mean arterial plasma peak concentration of 1.2 µg/ml with an individual maximum of 1.8 µg/ml. A peak venous plasma concentration of 2.07 µg/ml has been reported after 150 mg bupivacaine with added epinephrine injected intrapleurally after cholecystectomy (14). After bilateral intercostal nerve block with 400 mg bupivacaine (also with added epinephrine), a mean peak arterial plasma level is 3.29 µg/ml (15). The plasma levels reported in the present study after intrapleural administration are below the suggested convulsive plasma level of 4 µg/ml (16).

The frequency of successful analgesia was similar in three groups. In all but two patients complete pain relief was obtained within 15–30 minutes. The patient in group I in whom the effect was inadequate was extremely anxious and was given sedatives. These had satisfactory effect but an additional 20 ml 0.25 bupivacaine 30 minutes after the first injection did not result in complete pain relief, and the patient was given incremental doses of ketobemidon. Further local anesthetics were not given at that time because of the risk of side effects. But 20 ml of the 0.5% solution were administered approximately 7 hours after the first injection and effective pain relief was then achieved and lasted for 6.5 hours. This demonstrates that anxious patients may also require sedation and supplementary IM opioids.

The mechanism by which intrapleural local anesthetic relieves pain after a cholecystectomy is not clear. It has been suggested that reverse diffusion of local anesthetics occurs from the pleural to the subpleural space and then through to the thin muscles to reach a large number of intercostal spaces which are then blocked (6). The duration of analgesia showed a large interindividual variation in all groups. This has also been observed after intercostal blocks (17), particularly when long-acting agents such as bupivacaine are used (18).

In conclusion, we consider the intrapleural catheter technique to be an effective method of providing postoperative analgesia after unilateral upper abdominal surgery. Further studies are required to establish the optimal volume of the dosage of the local anesthetic.

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Effects of Etomidate, Midazolam, and Thiopental on Median Nerve Somatosensory Evoked Potentials and the Additive Effects of Fentanyl and Nitrous Oxide

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KOHT A, SCHÜTZ W, SCHMIDT G, SCHRAMM J, WATANABE E. Effects of Etomidate, Midazolam, and Thiopental on Median Nerve Somatosensory Evoked Potentials and the Additive Effects of Fentanyl and Nitrous Oxide. Anesth Analg 1988;67:435–41.

In 30 patients undergoing spinal disc operations, the effects of bolus injections followed by intravenous infusions of thiopental, etomidate, and midazolam on median nerve somatosensory-evoked potentials (SSEPs) were studied. Possible additive effects of fentanyl and nitrous oxide were also evaluated. Serial SSEP measurements were made before and for 25 minutes after the start of anesthesia. After induction with one of the three intravenous agents, fentanyl (10 μg/kg) was administered and SSEPs were again measured 1 and 5 minutes after administration. Sixty-five% nitrous oxide in 35% oxygen was administered after tracheal intubation and was followed by final SSEP measurements. The three intravenous agents affected SSEP signals differently. Etomidate increased both amplitude and latency. Thiopental decreased amplitude and increased latency. Midazolam had no effect on amplitude but increased latency. The addition of fentanyl and nitrous oxide had different effects in response to the three intravenous induction agents. This study emphasizes the differences in SSEP responses not only to different intravenous induction agents but also to the addition of fentanyl and nitrous oxide.

Key Words: ANESTHETICS, INTRAVENOUS—etomidate, thiopental, midazolam, fentanyl. BRAIN—somatosensory evoked potentials. HYPNOTICS, BENZODIAZEPINES—midazolam. ANALGESICS—fentanyl. ANESTHETICS, GASES—nitrous oxide.

Evoked potentials (EPs) have been used increasingly for intraoperative monitoring (1). Attempts have also been made to use them for measuring the depth of anesthesia (2), as well as for their more traditional use in the diagnosis of neurologic disorders (3). Somatosensory-evoked potentials (SSEPs) are used for intraoperative monitoring to detect neuronal hypoxia caused by retraction (4), hypoxemia (5), or the occlusion of blood vessels (6–8) and therefore to provide surgeons with early evidence of compromised neuronal function. SSEPs have proven useful in surgery for scoliosis (9,10), the spinal cord (11), and cerebral pontine angle tumors, during both intracranial and carotid vascular surgery (6), as well as for open heart surgery (12). The value of this method of monitoring depends on its ability to detect early changes in neuronal function and thus to prevent permanent neurologic deficits. Early SSEP changes include decreases in amplitude and increases in absolute and interpeak latencies. However, not all changes in SSEPs are related to surgical manipulations or tissue hypoxia. Up to 40% of all changes have been attributed to technical, physiologic, anesthetic, and pharmacologic causes (11). The value of SSEP monitoring increases as nonsurgical causes of SSEP changes are understood and controlled. The anesthetic agents etomidate, midazolam, and thiopental are used for both induction and maintenance of anesthesia and are also used in conjunction with nitrous oxide–narcotic techniques. The effects of etomidate and thiopental on SSEPs during the first few minutes of anesthesia have been evaluated (13), but their effects during later stages of anesthesia and the additive effects of fentanyl and nitrous oxide have not been studied. In this paper we report the initial effects of

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bolus injections and continuous infusions of etomidate, midazolam, and thiopental on median nerve somatosensory evoked potentials and the additive effects of fentanyl and nitrous oxide.

Methods

After obtaining written informed constant, 30 adult patients (ASA class 1 and 2, age 21–65 years) who were scheduled for lumbar disc surgery were studied according to a protocol approved by the committee on human research. Patients were included in the study if they were free of upper extremity neurologic abnormalities and had no contraindications to the withholding of preoperative medication. These patients were not given premedication and had any overnight fluid deficit replaced before induction of anesthesia. Disc recording electrodes were placed at C3', C4', and Fz according to the international EEG 10–20 system, as well as on the skin surface over the second vertebra. Impedances were kept below 2K ohms. Using silver surface electrodes, stimulation at the median nerve at the wrist was accomplished with 5.3-Hz, 0.2-msec constant current pulses at 1 mA above motor twitch. Three hundred-fifty responses were amplified, filtered (30–3000 Hz), and averaged on a Nicolet CA 1000 signal averager. After recording and replicating baseline SSEPs, patients were randomly classified into three groups of ten patients each. Patients in group 1 were given a 0.3 mg/kg bolus of etomidate followed by a 2 $mg \cdot kg^{-1} \cdot h^{-1}$ IV infusion of etomidate. Patients in group 2 were given a 0.3 mg/kg bolus of midazolam followed by a 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion of the midazolam. Patients in group 3 received a bolus injection of thiopental 5 mg/kg followed by a 2 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion of thiopental. These doses were used because of their clinical application during evoked potential monitoring. Patients who failed to lose consciousness or who regained consciousness during the study were given half of the original bolus dose of the drug initially injected. Patients' ventilation was assisted or controlled to maintain an end-expiratory CO_2 between 35 and 40 mm Hg as measured by a Siemens end-expiratory CO_2 monitor. Inhaled gases contained 35% oxygen in an air–oxygen mixture and 10-L total flow. After induction, the amount of muscle artifact decreased and the averaging procedure was changed to acquire 250 samples instead of 350 and an average was acquired every minute for 25 minutes (M25). In effect, continuous averages were acquired during the first 25 minutes, and each test served as a standard of comparison for the next recording.

At the end of M25 recording, all patients were given IV injections of fentanyl (10 $\mu g/kg$) and SSEP measurements were made 1 (Fent 1) and 5 (Fent 5) minutes later. Duplicate recordings were made at these times and for that reason Fent 1 reflects minutes 2 and 3 and Fent 5 reflects minutes 6 and 7 after the injection of fentanyl. During the period after fentanyl injection, patients were still breathing a mixture of air–oxygen as described above. After the Fent 5 recordings, patients received intravenous injections of succinylcholine to facilitate tracheal intubation. One set of SSEPs were collected during intubation (Tube) and another set immediately after intubation. After securing the oral endotracheal tube, a 10-L flow of 65% nitrous oxide and 35% oxygen replaced the air–oxygen mixture, and SSEPs were measured every minute for 10 minutes. Ventilation was controlled to maintain normal end expiratory CO_2. An oxygen analyzer was used on-line to assure appropriate delivery of oxygen, and blood pressure was monitored by an automatic blood pressure device placed at the nonstimulated arm. All data were stored on floppy diskettes for future analysis. Acquired data included the latency of N14, N20, central conduction time (CCT) (N20–N14), and the amplitude of N20–P23. Comparisons were made between data obtained at eight steps: baseline (T0); at T8, T16, T24 (each representing the average of eight values recorded the preceding 8 minutes); at Fent 1 and Fent 5; at Tube; and at $N20_5$ (average of minutes 6 and 7 after the start of nitrous oxide). Statistical methods included analysis of variance (ANOVA) between and within the groups to compare the effects of etomidate, midazolam, and thiopental on amplitude, latency, and CCT. The normal distribution for each group was tested by the Kolmogorov-Smirnov test and the homogeneity of the variances was tested by Bartlett's test. If homogeneity was not satisfied, a logarithmic transformation of the original data was carried out (this was done for amplitude). If ANOVA demonstrated a statistically significant effect, Scheffe's multiple range test was used to check for the differences. In addition, the eight steps in each group were evaluated in pairs by the *t*-test with the Bonferroni correction for multiple applications to the same data; the criterion for rejection of the null hypothesis was $P < 0.05$.

Results

Data obtained from all patients were satisfactory despite the absence of premedication. Six patients did not lose consciousness after the original injections and 12 patients required additional doses during the

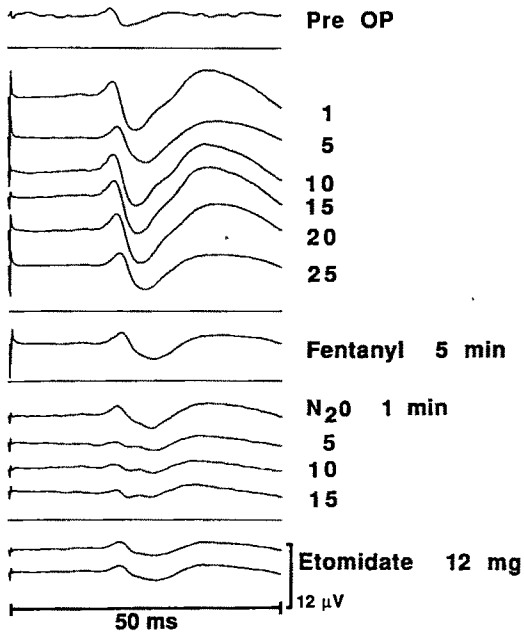

Figure 1. SSEP tracings during different steps of the study in a patient who had etomidate. Pre OP, preanesthesia baseline. Numbers indicate the minutes after which tracings were taken.

study period. These patients were distributed among all three groups (etomidate 3; midazolam, 4; and thiopental, 5).

The three groups were comparable in age, height, sex, and preanesthetic baseline values of SSEPs. Cardiovascular stability remained constant throughout the study.

Cortical responses to the three induction agents recorded at the various stages of the study are shown in Figures 1, 2, and 3. Figures 4 and 5 show average changes in cortical amplitude and CCT in the three groups during the various stages of the study. The mean and standard deviation for both cortical wave (N20) and cervical wave (N14) are shown in Tables 1 and 2. Table 3 contains data obtained during periods of the study in which differences between values reached a statistically significant level.

Etomidate had significant and consistent effects on both amplitude and latency of the cortical wave (N20) after induction of anesthesia and throughout the infusion period. Amplitude of the cortical wave N20–P23 increased to as much as 400% above baseline values, while the average amplitude of cervical responses slightly decreased. The average latency of cervical N14 increased slightly from 14.26 to 14.48 msec. The latency of cortical N20 increased from 20.09 to 21.44 msec. The CCT increased from 5.83 to 6.76 msec. Transmission time between N11 and N14 slightly decreased from 2.47 to 2.15 msec. These changes persisted to the end of the study although the amplitude changes gradually diminished. This

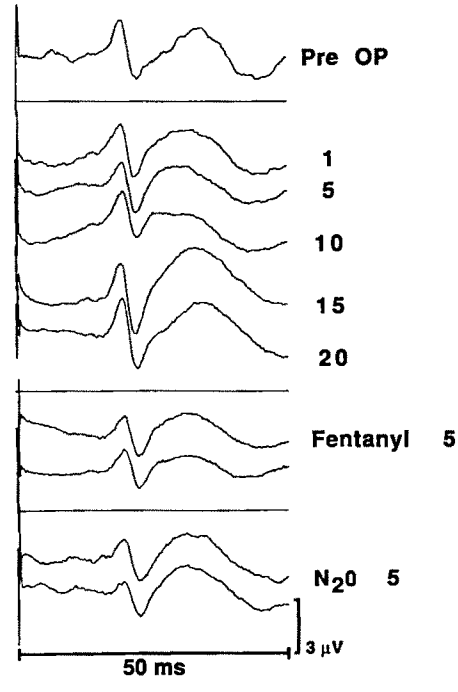

Figure 2. SSEP tracings during different steps of the study in a patient who had midazolam. Pre OP, preanesthesia baseline. Numbers indicate the minutes after which tracings were taken.

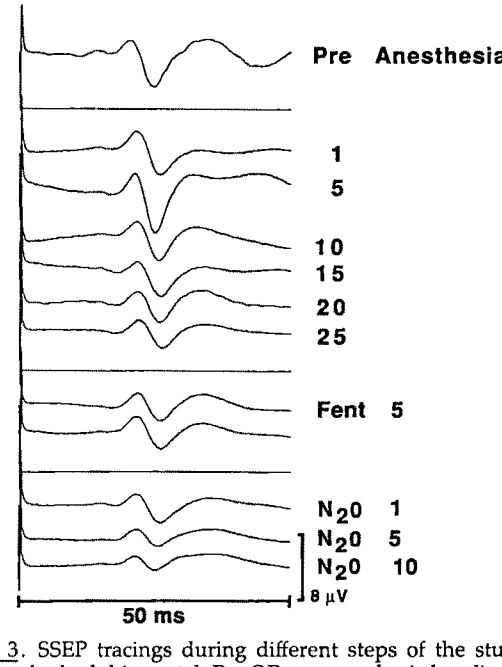

Figure 3. SSEP tracings during different steps of the study in a patient who had thiopental. Pre OP, preanesthesia baseline. Numbers indicate the minutes after which tracings were taken.

was probably due to a decreasing serum concentration of etomidate.

Thiopental had no significant effect on amplitude. The latency of N20 and CCT significantly increased in the first 8 minutes. No statistically significant increase in the latency of N14 was found in this group.

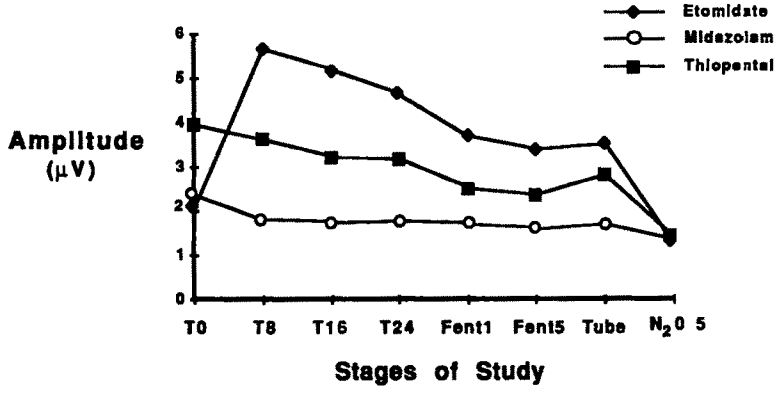

Figure 4. Amplitude of cortical wave N20 in the three groups during the different steps of the study. TO, preanesthesia baseline; T8, T16, T24, average of preceding 8 minutes; Fent 1, Fent 5; 1 and 5 minutes after fentanyl; tube, intubation; N_2O5: 5 minutes after start of nitrous oxide administration.

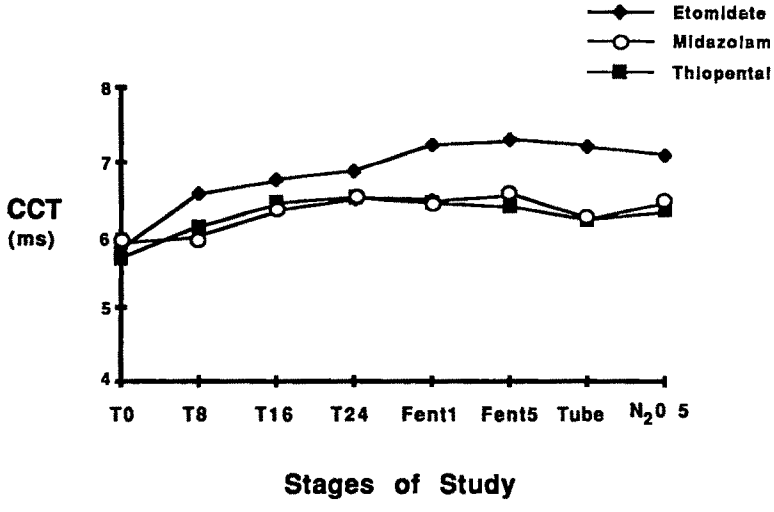

Figure 5. CCT in the three groups during different steps of the study. Abbreviations as in Figure 4.

Table 1. Mean and Standard Deviation of N20 for Etomidate, Midazolam, and Thiopental at the Various Stages of Study

N20 (msec)		T0*	T8	T16	T24	Fent 1	Fent 5	Tube	N_2O_5
Etomidate	$\bar{x}$	20.08	20.90	21.21	21.43	21.82	21.82	21.71	21.55
	SD	1.23	1.40	1.41	1.38	1.49	1.42	1.69	1.75
Midazolam	$\bar{x}$	19.53	19.66	20.09	20.37	20.41	20.49	20.30	20.35
	SD	0.99	0.95	0.96	1.01	0.90	0.87	0.80	0.85
Thiopental	$\bar{x}$	19.37	19.97	20.31	20.48	20.43	20.40	20.28	20.45
	SD	1.27	1.07	1.18	1.14	1.22	1.31	1.21	1.16

*Abbreviations: TO, preanesthesia; T8, T16, T24, average of preceeding 8 minutes; Fent 1, Fent 5; 1 and 5 minutes after fentanyl; tube; intubation; N_2O_5; 5 minutes after nitrous oxide.

Midazolam had no significant effect on the amplitude of the SSEP signals throughout the study. Cortical latency and CCT were not affected in the first 8 minutes after induction. However, a modest but statistically significant increase in the latency of N20 and CCT occurred between 8 and 16 minutes. No significant effect on the latency of N14 was found in this group. Although intubation decreased CCT and increased amplitude, these changes were not statistically significant.

When fentanyl was added to the induction agents, results varied. The addition of fentanyl to etomidate increased the latency of N20 and CCT but diminished the enhancing effect that etomidate had on the amplitude of N20–P23 wave. Cervical response was not significantly effected. The addition of fentanyl to midazolam had no significant effect. The addition of fentanyl to thiopental had no significant effect on latency or CCT, but did have an additional depressant effect on cortical amplitude.

Table 2. Mean and Standard Deviation of N14 for Etomidate, Midazolam, and Thiopental at the Various Stages of Study

N14 (msec)		T0*	T8	T16	T24	Fent 1	Fent 5	Tube	N_2O_5
Etomidate	$\bar{x}$	14.25	14.32	14.45	14.52	14.57	14.50	14.51	14.43
	SD	1.02	1.04	1.01	0.98	1.04	1.04	1.03	0.93
Midazolam	$\bar{x}$	13.62	13.66	13.75	13.86	13.93	13.93	14.07	13.89
	SD	0.87	0.82	0.85	0.84	0.83	0.87	0.56	0.73
Thiopental	$\bar{x}$	13.68	13.84	13.87	13.95	13.98	14.02	14.06	14.07
	SD	1.24	1.09	1.09	1.13	1.02	1.13	1.13	1.12

*Abbreviations as in Table 1.

Table 3. Statistical Analysis (*t*-test) of the Various Stages in the Three Groups for Amplitude and CCT

CCT (msec)	T0–T8*	T8–T16	T16–T24	T0–T24	T24–Fent 1	Fent 1–Fent 5	T24–Fent 5	Fent 5–Tube	Tube–N_2O_5	Fent 5–N_2O_5
Etomidate	†	†	NS	†	†	NS	†	NS	NS	NS
Midazolam	NS	†	NS	†	NS	NS	NS	NS	NS	NS
Thiopental	†	NS	NS	†	NS	NS	NS	NS	NS	NS
Amplitude (uV)	T0–T8	T8–T16	T16–T24	T0–T24	T24–Fent 1	Fent 1–Fent 5	T24–Fent 5	Fent 5–Tube	Tube–N_2O_5	Fent 5–N_2O_5
Etomidate	†	NS	NS	†	†	NS	†	NS	†	†
Midazolam	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Thiopental	NS	NS	NS	NS	NS	NS	NS	NS	†	†

*Abbreviations as in Tables 1 and 2.
†$P < 0.05$.

The addition of nitrous oxide did not significantly affect latency at N14, N20, or CCT in any group. However, amplitudes were depressed in all three groups. Amplitudes of the etomidate group were affected the most, whereas those of the midazolam group were affected the least. In fact, the amplitude depression in the midazolam group did not achieve statistical significance. Nonetheless, the net effect of nitrous oxide on amplitude was to eliminate the differences caused by induction agents and to bring the amplitude measurements to nearly identical endpoints.

Discussion

This study not only demonstrates the different effects of intravenous anesthetics on SSEP signals at different stages of anesthesia, but also demonstrates that such changes are affected differently by combinations of these intravenous anesthetics with either fentanyl or nitrous oxide. Such changes are not limited to amplitude but include cortical latency and CCT. Our results are in agreement with McPherson et al. (13), regarding the increase in amplitude after the injection of etomidate, but we were able to demonstrate the extended effects (enhancement of the signals) throughout the infusion period. The cause of such increases in amplitude is unknown. Because of the lack of increase in the amplitude of spinal responses, we agree with McPherson et al. (13) that such an increase would appear to originate from above the level of the spinal cord. The increases in amplitude were associated with increases in latency of both cortical and cervical responses. Although the increases in latency of the cervical responses were statistically significant, they were very small and do not compare to the increases in latency of the cortical responses. This is more apparent when observing the increases in CCT that reflect increases in conduction times of the area above the high spinal cord region. Such enhancement in amplitude may be helpful in patients with small cortical responses. However, the exaggerated depressant effect of the added fentanyl or nitrous oxide should be kept in mind. Enhancement of cortical amplitude can best be achieved by a continuous intravenous infusion of etomidate and avoidance of nitrous oxide during critical periods of surgery. The decline in amplitude associated with addition of fentanyl during the use of etomidate is statistically significant even though absolute values remain above preanesthetic levels. The use of etomidate as a diagnostic tool during the loss of cortical SSEPs or as an enhancing agent requires further investigation.

The results of our study are in agreement with those of McPherson et al. (13) regarding the absence of effects of thiopental on the amplitude of cortical responses, while increasing cortical latency and CCT. Body temperature remained stable during our study,

suggesting that the increase in cortical latency was not due to hypothermia. However, because differences may exist between central body temperature and the temperature of the extremities, it is possible to have effects on SSEPs related to local hypothermia in a normothermic patient. To detect these increases in peripheral conduction time, SSEPs could be recorded at Erb's point as well. This was not done in our study, but the small increase in latency of the cervical spinal responses with a significant increase of CCT does not support hypothermia-related increases in conduction times of the upper extremities as being significant. The increases in latencies of both the N20 and the CCT is in agreement with changes seen in barbiturate coma (14,15), although in our study such increases were limited to the first 16 minutes of thiopental infusion.

The effects of midazolam on SSEPs are similar to those of thiopental, but there are some differences. For instance, there is a delayed increase of CCT caused by midazolam as compared to an early increase caused by thiopental. Also, there is a lack of any effect of a combination of fentanyl and midazolam or a combination of fentanyl, nitrous oxide, and midazolam on the amplitude of recorded cortical waves compared with a depressant effect of fentanyl–thiopental or fentanyl, nitrous oxide, and thiopental combinations. Such differences may suggest possible advantages of the use of midazolam over thiopental.

In this study, fentanyl, which has little effect on SSEP signals when given alone (12,16), had a significant effect on amplitude, latency or both when given in conjunction with other drugs. Although the addition of fentanyl did not affect signal amplitude or latency in patients who received midazolam, it did significantly affect both amplitude and latency in patients given etomidate and only affected amplitude but not latency in patients given thiopental. Such differences in effects may explain the findings reported by various workers in this field. These differences in effects are of obvious importance when planning anesthesia for patients undergoing SSEP monitoring.

The results we obtained regarding the depressant effects of nitrous oxide on the amplitude of cortical responses are in agreement with others (17–19). However, this effect ranged from a 62% decrease in amplitude in the etomidate group to a 40% decrease in the thiopental group, to a mere 16% nonsignificant decrease in patients given midazolam. When comparing the mean values of the N20–P23 amplitudes, it is of interest that nitrous oxide variably decreased the amplitudes in all three groups but brought them to equivalent endpoints as seen in Figure 4.

In this study we set out to compare the effects of commonly used doses of etomidate, midazolam, thiopental, fentanyl, and nitrous oxide rather than comparing the dose–response curve for these agents. We can not say with certainty if such observations can be related to all points on the distribution curve. Further work is needed to determine if such effect exists.

In summary, the three anesthetic induction drugs we studied differ in their effects on SSEP signals. Midazolam has little effect on amplitude but is associated with late (8–16 minutes) increases in cortical latencies and CCT. Thiopental has little effect on amplitude but has an early (after 1 minute) increase of cortical latency and CCT. Etomidate increases amplitude, cortical latency, and CCT. Such increases in amplitude (enhancement) may be helpful when performing intraoperative monitoring of patients with small cortical signals. The different changes caused by the three agents are further complicated when fentanyl or nitrous oxide are added. It is essential to understand these complex effects when interpreting intraoperative SSEPs.

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Invasive and Noninvasive Measurement of the Respiratory Deadspace in Anesthetized Children with Cardiac Disease

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FLETCHER R. Invasive and noninvasive measurement of the respiratory deadspace in anesthetized children with cardiac disease. Anesth Analg 1988;67:442–7.

To compare the magnitude of the different "invasive" and "noninvasive" dead space variables and the effect on them of ventilator setting, CO_2 single breath tests (SBT-CO_2) were obtained using an on-line computerized system based on the Servo ventilator and CO_2 Analyzer 930, in 50 children anesthetized for cardiac surgery. The variables were the airway deadspace (V_Daw), Bohr's deadspace (V_DBohr) obtained noninvasively using end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) for alveolar P_{CO_2} in the deadspace equation, and the physiologic deadspace, V_Dphys. In 42 children with normal single breath tests, V_Daw was two-thirds of V_DBohr; in 9 children in whom phase III of SBT-CO_2 (the "alveolar plateau") was steeper than normal, it was only half of V_DBohr. Steeper slopes of phase III were seen particularly in the present of left–right (LR) shunting. V_Dphys was very similar in magnitude to V_DBohr in all children, except those with right–left (RL) shunts. V_Daw was the major component of V_Dphys only in children with normal arterial–end-tidal P_{CO_2} differences, i.e., those without RL shunts. When two ventilator frequencies giving the same alveolar ventilation were compared in children with normal gas exchange, V_DBohr as a fraction of tidal volume was least at the lower frequency, as it also is in adults. The data confirm that noninvasive CO_2 monitoring and measurement of deadspace gives useful indexes of the adequacy of ventilation in all children except those with RL shunts.

Key Words: ANESTHESIA—pediatric. LUNG—deadspace in children. HEART—cardiac disease and respiratory dead space.

During anesthesia with intermittent positive pressure ventilation (IPPV) in children, continuous monitoring of expired CO_2 offers a noninvasive guide to the adequacy and efficiency of ventilation. In particular, the airway deadspace (V_Daw) and Bohr's deadspace (V_DBohr) can be calculated. Simultaneous "invasive" sampling of arterial blood and measurement of its CO_2 tension ($Paco_2$) allows the physiologic deadspace (V_Dphys) to be estimated.

Figure 1 explains the relation between the three deadspace terms. The figure is based on the single breath test for CO_2 (SBT-CO_2) (1), which is the plot of expired CO_2% or P_{CO_2} against expired volume. The curve has three parts: phase I represents the CO_2-free gas from the airway, the phase II, the rapid S-shaped upswing, represents the "progressive recruitment of transit times" (2) as alveolar gas begins to appear in the airway. Phase III, sometimes called the alveolar plateau, represents alveolar gas. V_Daw represents the volume of the convective airway deadspace from the airway opening to the alveolar/fresh gas interface (1). V_DBohr is obtained using end-tidal CO_2 ($P_{ET_{CO_2}}$) for alveolar P_{CO_2} in Bohr's equation (3,4).

$$\frac{V_DBohr}{V_T} = 1 - \frac{P\bar{E}_{CO_2}}{P_{ET_{CO_2}}} \quad (1),$$

where V_T is tidal volume. V_Dphys is obtained from

$$\frac{V_Dphys}{V_T} = 1 - \frac{P\bar{E}_{CO_2}}{Paco_2} \quad (2),$$

where $P\bar{E}_{CO_2}$ is mixed expired P_{CO_2}.

It can be seen from Figure 1 that the extent to which V_DBohr exceeds V_Daw depends on the slope of phase III. When phase III has a positive slope, which it has as a rule, V_DBohr includes part of the alveolar deadspace (see later). The phase III slope is increased in most forms of lung disease (1), and also by left-to-right intracardiac shunting (5), which increases the flow of blood through the lung. V_Dphys includes not only the airway deadspace, but also the alveolar

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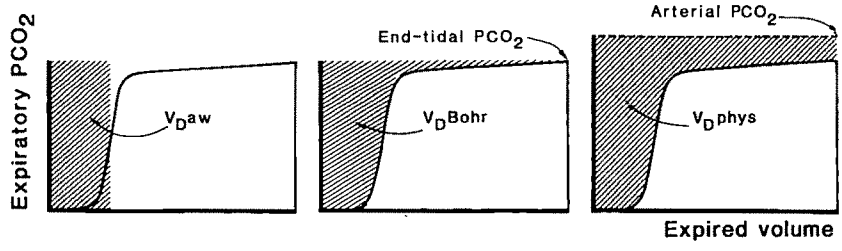

Figure 1. Schematic CO_2 single breath tests, showing the relation between V_DAW (left panel), V_DBohr (middle panel), and V_Dphys (right panel). V_DBohr contains, in addition to V_DAW, part of the alveolar deadspace. The rest of the alveolar deadspace is responsible for the difference between V_DBohr and V_Dphys. The roughly linear right-hand part of the tracing (the somewhat inappropriately named "alveolar plateau") is also known as phase III of the single breath test.

deadspace, (represented by the area between the $Paco_2$ value and phase III.) The extent to which V_Dphys exceeds V_DBohr depends on the arterial–end-tidal Pco_2 difference ($Paco_2 - P_{ET_{CO2}}$).

The arterial–end-tidal Pco_2 difference is close to zero in normal children (4,5), and it therefore follows that V_DBohr and V_Dphys must be similar in magnitude. For this reason, Bohr's deadspace has been frequently used by pediatric anesthesiologists to avoid arterial blood sampling. However, in cyanotic heart disease, where $P_{ET_{CO_2}}$ is considerably less than $Paco_2$, V_DBohr must be less than V_Dphys.

The purpose of the present paper is to analyze the relation between the three deadspace terms in children with normal and abnormal pulmonary circulation. The effect of the shape of SBT-CO_2 on these relations will be discussed.

Methods

Some deadspace data from 41 of the children have previously been published (5), although not in the form in which they now appear. The patients were 50 children (age range 3 months–9 years; median 2.4 years) undergoing open or closed cardiac surgery. On the basis of their preoperative investigations (cardiac catheterization or echocardiography, chest X-ray, and haemoglobin levels), they were classified into four groups: 13 with normal pulmonary circulation, 15 with left-to-right (LR) shunting, 14 with right-to-left (RL) shunting, and 8 with mixed shunts. Patients over 1 year of age were premedicated with a mixture of apozepam, morphine, and scopolamine, given rectally. Anesthesia was provided with N_2O, 50% in O_2, and fentanyl. Those undergoing open heart surgery also received droperidol; those undergoing surgery for closure of a patent ductus arteriosus or correction of coarctation received 0.5% halothane. No child received any vasoactive drugs, and none had overt heart failure or chest infections. Atropine or muscle relaxants had not recently been given to any children at the time of measurement.

SBT-CO_2 was obtained using an on-line computer connected to a Servo ventilator 900 C and CO_2 Analyzer 930 (5,6,7). The computer received signals for airway flow and pressure and timing signals from the ventilator. It received a signal for expired CO_2 from the CO_2 analyzer. The CO_2 analyzer was calibrated daily against a test gas containing CO_2 in equal parts N_2O and O_2, and this test gas was checked against the blood gas analyzer by tonometry.

Measurements were made at steady state, with the patients in the supine position, during undisturbed anesthesia. Arterial blood from an indwelling femoral or radial artery cannula was sampled slowly while the computer sampled three breaths. Body temperature was measured in the esophagus and $Paco_2$ was corrected to this temperature.

In 16 children with normal pulmonary circulation or LR shunts, measurements were made at two ventilator settings. In a randomized sequence, ventilatory frequency was reduced and tidal volume increased, or vice versa, in such a way as to keep CO_2 minute elimination constant. All measurements were made using constant flow inspiration, 25% of cycle time with an end-inspiratory pause of 10%.

Gas exchange variables obtained included V_DBohr (Eq. 1), V_Dphys (Eq. 2), V_DAW (defined as the point of inflexion in phase II, the rapid upswing in SBT-CO_2) and the slope of phase III, sometimes called the alveolar plateau. The phase III slope was obtained as "Bohr's alveolar deadspace fraction," calculated from

$$(V_DBohr - V_DAW)/(V_T - V_DAW),$$

where V_T is tidal volume. Statistical comparisons were made using paired and unpaired *t*-tests.

Results

Figure 2 shows typical single breath tests from children with normal pulmonary circulation and with both kinds of shunt.

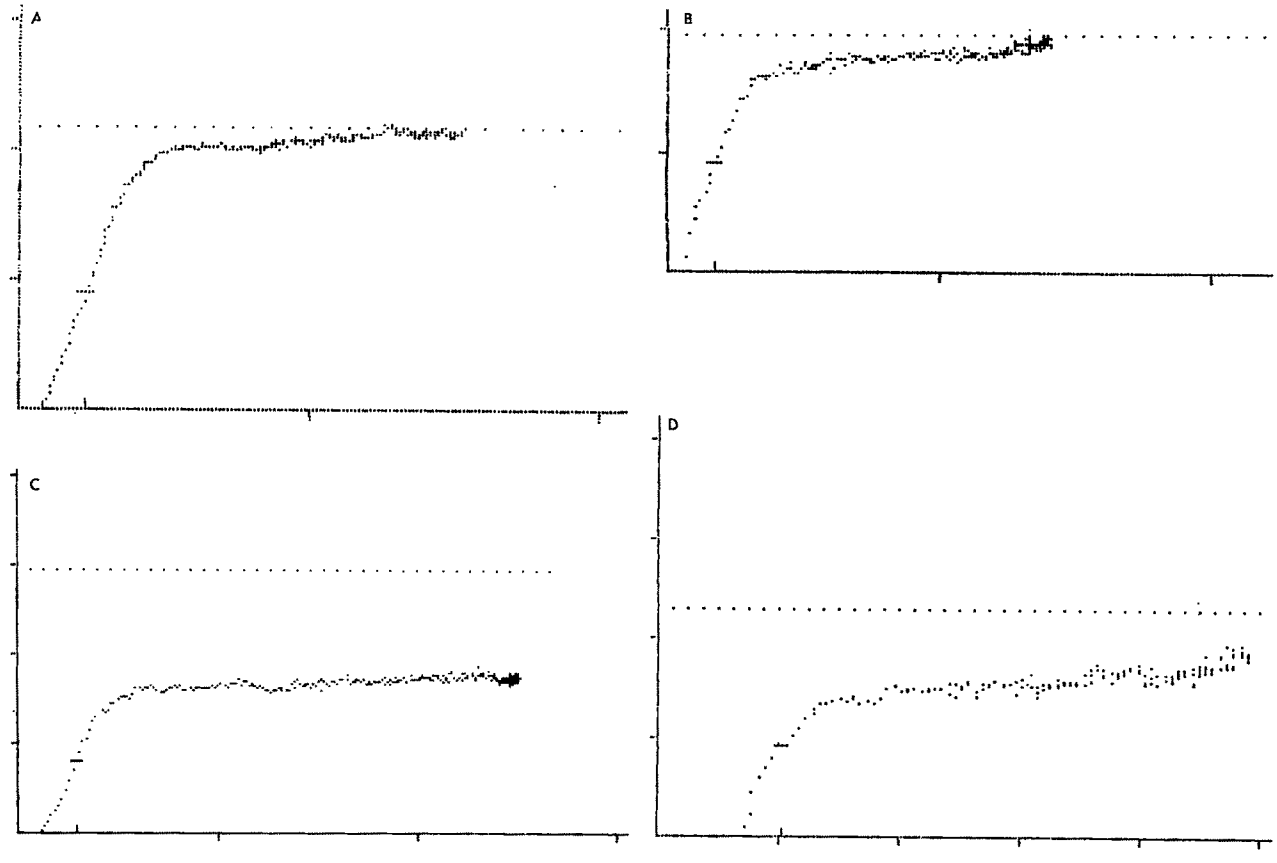

Figure 2. CO_2 single breath tests from children with **(A)** normal pulmonary circulation, **(B)** L-R shunt, **(C)** R-L shunt, **(D)** mixed shunt. The volume axis is marked 5, 10, 15%, etc. of predicted total lung volume. The markings on the vertical axis are 2, 4, 6, and 8% CO_2. The computer has marked in V_Daw with a short horizontal line in phase II and also on the volume axis. Observe the increase in phase III slope in **(B)** and **(D)**, secondary to pulmonary overcirculation. In **(C)**, phase III is extremely flat, but there is a large alveolar deadspace. **(D)** Shows both the large alveolar deadspace on R-L shunting and the increased phase III slope of L-R shunting. Figure reproduced in part from (5) with the editor's permission.

Airway Deadspace and V_DBohr

For the entire material, the relation between V_DBohr and V_Daw (Fig. 3) is given by

$$V_Daw\ (ml) = 0.01 + 0.648 \times V_DBohr\ (ml);$$

residual standard deviation

$$(RSD) = 3.0, \quad r = 0.95, \quad P < 0.0001.$$

All the points lie under the line of identity, i.e., V_DBohr is always greater than V_Daw. The patients whose values lie furthest from the line of identity have increased slopes of phase III of SBT-CO_2. Thus, there was a strong negative correlation ($r = -0.76$, $P < 0.0001$) between the ratio V_Daw/V_DBohr and the slope of phase III. In 41 children in whom the slope of phase III was within two SD of normal (3), V_Daw was $67 \pm 7\%$ of V_DBohr. In the remainder, most of whom had LR or mixed shunts, it was $51 \pm 8\%$ ($P < 0.001$). There was no difference in the V_Daw/V_DBohr relation between normal children and those with RL shunts. There was no correlation between V_Daw/V_DBohr and tidal volume.

Arterial P_{CO_2} and End-Tidal P_{CO_2}

In children with normal pulmonary circulation, and those with LR shunting, $Paco_2 - P_{ET_{CO_2}}$ was not significantly different from zero ($P = 0.4$, $P = 0.9$). In children with pure RL shunting, $Paco_2 - P_{ET_{CO_2}}$ was 2.2 – 15.1, mean 7.7 mm Hg ($P < 0.0001$); in those with mixed shunts, it was −1.8 – 6.2, mean 1.9 mm Hg ($P = 0.08$).

Physiologic Deadspace and V_DBohr

As follows from the above, the ratio V_DBohr/V_Dphys was close to unity (1.01 ± 0. 11) in children with normal circulation and in those with LR shunting. In

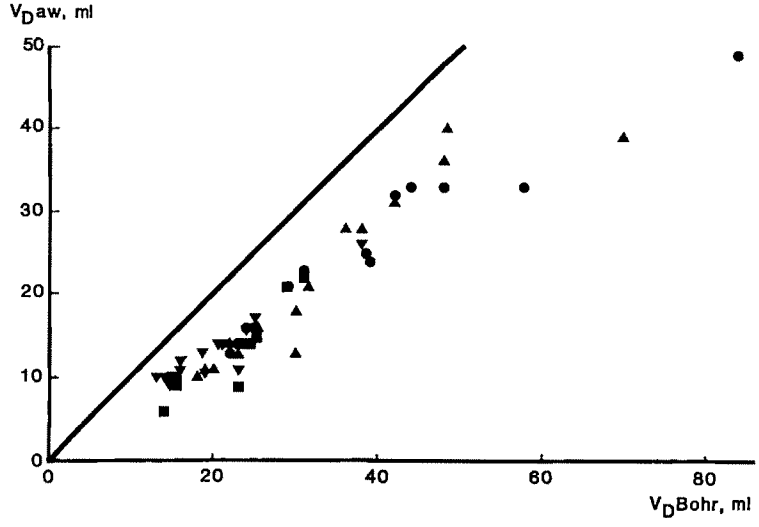

Figure 3. Airway deadspace related to V_DBohr. Key: ●, normal circulation; ▲, LR shunting; ▼, RL shunting; ■, mixed shunting. The line of identity, y = x, is shown.

children with pure RL shunting, the V_DBohr/$V_D$phys ratio was 0.60 ± 0.13 (difference from unity, $P < 0.0001$); with mixed shunting it was 0.85 ± 0.16 ($P < .05$).

Airway Deadspace and $V_D$phys

In normal children and in those with LR shunting, $V_D$aw was the chief (65 ± 11%) component of $V_D$phys. As with $V_D$aw/V_DBohr, the ratio $V_D$aw/$V_D$phys was negatively correlated to phase III slope ($r = -0.46$, $P = 0.001$). In children with mixed RL–LR shunts, $V_D$aw was half $V_D$phys (48 ± 10%); in those with RL shunts, it was less (38 ± 9%).

Effect of Changing Ventilator Setting

In 16 children, mean ventilatory frequency was changed from 29 to 21 per minute or vice versa and mean tidal volume was also adjusted from 113 to 153 milliliters so that mean CO_2 elimination, and therefore alveolar ventilation, remained unchanged ($P = 0.3$). The mean value of $V_D$aw/V_DBohr was insignificantly less at the lower frequency; 0.61 vs 0.65, $P = 0.1$. However, V_DBohr/V_T was significantly less, i.e., the efficiency of gas exchange improved, at the lower frequency (0.19 vs 0.22, $P < 0.0001$).

Effect of Halothane on $V_D$aw

There was no significant difference in the relation between $V_D$aw/height or $V_D$aw/age in children who had received halothane and those who had not.

Discussion

In this study as in others (1,8), children with normal pulmonary circulation and those with LR shunting have extremely good lung function by adult standards. Both the physiologic deadspace fraction and $Paco_2 - P_{ET_{CO_2}}$ were smaller than in adults (9). The slope of phase III of SBT-CO_2 was small in most children. The main exceptions were some with large LR shunts or mixed shunts with a large LR component. The cause of the increased slope in LR shunting is an increased spread of ventilation/perfusion ratios secondary to increased pulmonary flow or pressure (5). It is associated with a moderate reduction in Pao_2.

The $V_D$aw/V_DBohr relation is affected by the slope of phase III. V_DBohr consists of the airway deadspace plus part of the alveolar deadspace (Fig. 1). The magnitude of the alveolar part of V_DBohr is proportional to phase III slope. (In fact, phase III slope was measured in this way; see Methods.) Thus, in children with normal slopes, $V_D$aw was 67% of V_DBohr. In children in whom phase III slope was increased, $V_D$aw was only 51% of V_DBohr. RL shunting has no effect on the $V_D$aw/V_DBohr relation, because it does not give rise to an increased slope. In adults, who often have steep phase III slopes, the difference between $V_D$aw and V_DBohr can be much greater, especially at large tidal volumes (10).

Figure 1 suggests to the eye that $V_D$aw is more than 67% of V_DBohr. However, V_DBohr and $V_D$phys, but not $V_D$aw, are influenced by the rebreathing of expired gas from the apparatus Y-piece. Rebreathing effectively diminished tidal CO_2 elimination; if correction is not made for this, V_DBohr is underestimated to an extent depending on the ratio of the rebreathed volume to tidal volume.

Table 1. Summary of Patient Data

	Age (Year)	V_Daw/V_DBohr	V_DBohr/V_Dphys	V_Daw/V_Dphys	$PaCO_2-P_{ET}CO_2$ (mmHg)
Children with normal pulmonary circulation					
1. PS	1.9	0.72	0.96	0.69	−0.8
2. AS	4.8	0.75	0.88	0.66	1.3
3. PS	5.8	0.61	1.22	0.74	−0.6
4. PS	3.5	0.67	0.85	0.57	1.1
5. AS, PS	0.9	0.59	1.10	0.65	−0.1
6. PDA, normal chest x-ray	7.0	0.57	1.08	0.61	−1.6
7. PDA, normal chest x-ray	8.9	0.62	0.95	0.58	0.5
8. PDA, normal chest x-ray	6.8	0.65	1.15	0.75	−1.4
9. Coarctation of aorta	5.8	0.76	0.91	0.69	0.4
10. PDA, normal chest x-ray	1.5	0.64	1.04	0.66	−0.7
11. AS	6.5	0.74	0.96	0.72	0.6
12. PDA, normal chest x-ray	14.4	0.58	1.09	0.64	−0.5
13. Coarctation of aorta	5.0	0.69	1.22	0.84	−1.6
Mean	5.6	0.66	1.03	0.68	−0.3
SD	3.5	0.07	0.12	0.07	1.0
Children with L-R shunts					
14. VSD, shunt 3:1, cardiomegaly, widened pulmonary vessels	3.9	0.74	1.04	0.76	−1.5
15. ASD, shunt 2.4:1, cardiomegaly, widened pulmonary vessels	6.3	0.75	0.95	0.71	0.2
16. ASD, VSD, shunt 3:1, cardiomegaly, widened pulmonary vessels*	0.8	0.58	0.92	0.53	0.4
17. ASD, cardiomegaly, widened pulmonary vessels	5.2	0.60	0.79	0.48	1.7
18. ASD, shunt 3:1, cardiomegaly, widened pulmonary vessels	5.3	0.74	0.99	0.73	−1.1
19. VSD, PDA, shunt 2.8:1, cardiomegaly, widened pulmonary vessels	1.2	0.64	1.01	0.64	−0.8
20. VSD, pulmonary hypertension	0.8	0.55	0.94	0.52	0.7
21. ASD, shunt 2:1*	11.0	0.56	0.97	0.54	0.4
22. ASD	7.3	0.83	1.00	0.82	0.2
23. ASD, shunt 3:1	4.7	0.78	0.82	0.64	2.6
24. PDA, widened pulmonary vessels	4.6	0.67	1.08	0.72	−1.2
25. PDA, widened pulmonary vessels*	1.4	0.57	1.35	0.76	−2.2
26. PDA, widened pulmonary vessels	6.1	0.64	0.83	0.53	0.9
27. PDA, widened pulmonary vessels	1.2	0.56	1.21	0.67	−1.7
28. PDA, 2:1 shunt*	1.1	0.43	0.88	0.38	2.1
Mean	4.1	0.64	0.98	0.63	0.1
SD	3.0	0.11	0.15	0.13	1.4
Children with R-L shunting					
29. Single ventricle, PS	4.4	0.67	0.51	0.34	7.0
30. Fallot's tetralogy	3.2	0.68	0.81	0.55	2.0
31. PS, ASD	2.4	0.67	0.77	0.52	2.3
32. PA	0.8	0.75	0.45	0.34	12.3
33. Fallot's tetralogy	0.3	0.77	0.60	0.46	2.3
34. TGA	0.6	0.69	0.69	0.47	4.7
35. Fallot's tetralogy	3.8	0.71	0.63	0.45	3.2
36. TGA	0.8	0.60	0.52	0.31	6.3
37. Single ventricle, MA	0.2	0.70	0.41	0.29	15.1
38. TGA	0.3	0.67	0.41	0.27	12.7
39. PS, VSD, DORV*	1.5	0.48	0.55	0.26	12.0
40. TGA	5.2	0.68	0.57	0.39	11.4
41. PA*	0.9	0.58	0.70	0.41	3.3
42. PS, ASD, DORV	1.0	0.68	0.48	0.33	13.6
Mean	1.9	0.67	0.58	0.38	7.7
SD	1.7	0.07	0.13	0.09	4.9
Children with mixed shunts					
43. VSD, TGA*	0.6	0.60	0.75	0.45	4.6
44. AVC*	0.7	0.43	1.10	0.47	−1.8
45. "Acyanotic Fallot"	0.7	0.58	0.92	0.53	0.3
46. "Acyanotic Fallot"*	1.5	0.58	0.66	0.39	3.2
47. Fallot's tetralogy	2.7	0.61	0.80	0.48	1.9
48. AVC, PDA	1.4	0.67	0.67	0.45	6.2
49. "Acyanotic Fallot"	4.3	0.72	0.95	0.69	0.7
50. VSD, PDA*	0.3	0.38	1.00	0.38	0.0
Mean	1.5	0.57	0.86	0.48	1.9
SD	1.4	0.11	0.16	0.10	2.6

* Patient with phase III slope 2 SD or more greater than normal.

Abbreviations: PS, pulmonary stenosis; AS, aortic stenosis; PDA, patent ductus arteriosus; VSD, ASD, ventricular, atrial septal defect; TGA, transposition of the great arteries; PA, pulmonary atresia; MA, mitral atresia; DORV, double outlet, right ventricle. AVC, common atrio-ventricular canal.

The V_DBohr/$V_D$phys relation depends solely on the $Paco_2 - P_{ET_{CO_2}}$ difference. $V_D$phys and V_DBohr are very similar in all children except, as could be predicted, those with increased $Paco_2 - P_{ET_{CO_2}}$ differences, i.e., those with RL or mixed shunts. Clearly, $P_{ET_{CO_2}}$ cannot be used as an estimate of $Paco_2$ in these children, nor can V_DBohr be used as an estimate of $V_D$phys. Furthermore, any measurement of alveolar ventilation based on V_DBohr ($\dot{V}_A$Bohr) will be an overestimate (3,11).

The use of $P_{ET_{CO_2}}$ as a measure of $Paco_2$ is also problematic in most middle-aged and elderly patients (9,12,13), but in these it is a result of the spread of ventilation/perfusion ratios secondary to acquired airways disease, rather than true RL shunting. In airways disease, because of the steep phase III slope, $Paco_2 - P_{ET_{CO_2}}$ is strongly tidal volume dependent; the greater the tidal volume, the smaller the CO_2 difference. This is not the case in RL shunting.

In normal children and most with LR shunts, $V_D$aw was the major component of $V_D$phys and V_DBohr; this is not so in adults (9). $V_D$aw/V_DBohr was not affected by changing ventilator setting, but V_DBohr/V_T decreased when tidal volume was increased. These findings parallel those in adults, in whom the efficiency of gas exchange is also greater at lower ventilatory frequencies (9). Provided its limitations in the presence of R-L shunting are understood, expired CO_2 monitoring offers a useful way of quantifying gas exchange during anesthesia in children.

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Halothane Hepatotoxicity and Reductive Metabolism of Halothane in Acute Experimental Liver Injury in Rats

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Halothane hepatotoxicity and reductive metabolism of halothane in acute experimental liver injury in rats.
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Reductive metabolism of halothane was measured after acute liver injury induced by galactosamine (1.0 g/kg, IP) in rats. On the seventh day of liver injury, when previously elevated serum alanine aminotransferase levels had returned to near normal range, anaerobic release of fluoride from halothane by hepatic microsomes, which appears to reflect the reductive pathway of halothane metabolism, was still remarkably decreased (1.36 ± 0.56 nmol/mg protein/h vs 5.88 ± 0.58 in controls, $P < 0.001$). In another set of experiments, rats ($n = 8$) given galactosamine 7 days earlier and saline-treated control rats were given halothane anesthesia (1.0%) under mildly hypoxic conditions ($F_{I_{O_2}}$ 0.14). In saline controls, halothane anesthesia resulted in a mild but statistically significant increase in serum alanine aminotransferase levels (32 ± 4 vs 59 ± 6 U/ml, $P < 0.001$). In contrast, serum levels of this enzyme were not changed by halothane anesthesia in galactosamine-treated rats (45 ± 3 vs 49 ± 4 U/ml). Although care should be taken in extrapolating the importance of these animal data to humans, the results of this study suggest that halothane hepatotoxicity can be attenuated in the presence of minor liver injury as a result of decreased hepatic biotransformation of the anesthetic. The data support the view that halothane anesthesia is not necessarily contraindicated in subjects with impaired liver function.

Key Words: ANESTHETICS, VOLATILE—halothane. LIVER—hepatic toxicity. TOXICITY—halothane.

Clinical tradition would have it that preexisting hepatic injury may enhance susceptibility to hepatotoxic effects of drugs and other chemicals. Evidence for this, however, is scant (1). Halothane may have hepatotoxic potential in some circumstances, and it has been postulated that the toxicity may at least in part be mediated by reductive metabolites of the anesthetic (2–4). Recently, the view that halothane anesthesia is not necessarily contraindicated in patients with chronic liver disease has been advanced (5,6). However, it is not clear whether preexisting acute liver injury alters susceptibility to the hepatotoxic potential of halothane. In the present study, we examined the effect of acute liver injury induced by galactosamine (GalN) on the reductive metabolism of halothane in rats to evaluate whether preexisting liver disease may predispose to halothane hepatotoxicity in rats.

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Methods

Animal Procedures

A total of 58 250-g male Sprague-Dawley rats (Takasugi Animal Center, Saitama, Japan) were used. All rats were housed in screen-bottomed cages under controlled lighting (12 hours light:12 hours dark) and temperature (21 ± 1°C); they were fed a commercial diet (MF; Oriental Yeast Co., Ltd., Tokyo) and water ad libitum. All rats fasted overnight before being killed or receiving halothane anesthesia.

Experiment 1

A time course of GalN-induced liver injury at a dose of 1.0 g/kg was assessed. Eight rats received a single intraperitoneal injection of D-galactosamine hydrochloride (1.0 g/kg in a neutralized solution). Blood samples (0.2 ml) were taken from the retroorbital sinus for measurement of serum alanine aminotransferase (SALT) levels 2, 3, 7, and 14 days after the GalN treatment.

Experiment 2

Reductive metabolism of halothane, together with two representative hepatic microsomal cytochrome P-450–dependent reactions, were assessed during the course of acute liver injury. At 0, 3, 7, and 14 days after the injection of GalN as in experiment 1, rats were killed by decapitation (six rats of each period after GalN treatment). The liver was quickly removed, and the microsomal fraction of the liver was obtained by differential centrifugation as described previously (7). Final microsomal preparations were suspended in 0.1 M potassium phosphate buffer (pH 7.4), stored at −80°C, and used for the microsomal assays described below within 2 days.

Experiment 3

Twenty rats were classified into two groups. Ten were given GalN as described earlier and the rest received saline only. Serial blood samples (0.2 ml) were taken from the retroorbital sinus 2, 3, and 7 days after each injection for SALT determinations. On the seventh day, the rats were exposed to halothane anesthesia (1.0%) under mildly hypoxic conditions ($F_{I_{O_2}} = 0.14$) for 2 hours as described previously (8). After anesthesia, the rats were returned to their metal cages. Blood was taken 24 hours later.

Microsomal Assays

Aminopyrine N-demethylase activity was determined in a 3-ml incubation mixture comprising 6 mM $MgCl_2$, 0.4 mM NADPH, 0.1 M potassium phosphate buffer (pH 7.4), 3 mg microsomal protein, and 8 mM aminopyrine. After incubation at 37°C for 5 minutes, the reaction was stopped by adding 1 ml of 10% trichloroacetic acid. Formaldehyde (HCHO) produced during the demethylation process of aminopyrine was then measured using the procedures described by Nash (9). Aniline hydroxylase activity was measured after the formation of para-aminophenol from aniline. The incubation mixture (3 ml) contained 6 mM $MgCl_2$, 1 mM Na_2-EDTA, 0.4 mM NADPH, 0.1 M potassium phosphate buffer (pH 7.4), 3 mg of microsomal protein, and 8 mM aniline. The mixtures were incubated at 37°C for 10 minutes, and the reaction was stopped by adding 1 ml of 10% trichloroacetic acid. The production of para-aminophenol was measured as outlined by Imai et al. (10).

To assess the reductive metabolism of halothane, the release of fluoride from halothane was determined using microsomes incubated under nitrogen as described by Van Dyke and Gandolfi (11). The reaction mixture (final volume, 5 ml) contained 250 μmol of Tris–HCl (pH 7.4 at 37°C), 5 μmol Na_2-EDTA, 2 μmol NADPH, 4 μL halothane, and microsomes (18 mg of protein). The reaction was started by adding NADPH and carried out at 37°C under nitrogen. Anaerobic conditions were achieved by pregassing the reaction mixture for 3 minutes with prepurified nitrogen, which contained less than 1 ppm oxygen (Nippon Sanso Ltd., Tokyo). After 7.5 and 15 minutes, the reaction was stopped by 5 ml of 0.2 M acetate containing 1.5 μmol of potassium chloride and 0.28 μmol of sodium citrate. Fluoride determinations were performed using an Iwaki fluoride electrode (TM008, Iwaki Glass, Inc., Tokyo), a reference electrode, and a millivoltmeter.

Other Biochemical Procedures

Hepatic microsomal cytochrome P-450 contents were measured using the method of Omura and Sato (12). The protein concentration was determined by the method of Lowry et al. (13) with bovine serum albumin as a standard. SALT levels were measured using sigma GPT kits (GO & GP transaminase kit, no. 505-OP, Sigma Chemical Co., St. Louis, MO). Results were expressed in terms of (Sigma-Frankel) units per milliliter.

Miscellaneous

Halothane was purchased from Hoechst Japan Co., Ltd., Tokyo, and D-galactosamine hydrochloride from Nakarai Chemicals, Ltd. (Kyoto). All other reagents were obtained from standard chemical sources.

All values were expressed as mean ± SEM. The statistical significance of the differences between groups was assessed by the nonpaired Student's *t*-test. The study was approved by the animal investigation committee of Chiba University School of Medicine.

Results

Experiment 1

Serum alanine aminotransferase levels during a course of GalN-induced acute liver injury in eight rats are shown in Figure 1. The range of values obtained 2 days after injection was 45 to 4680 U/ml. The levels

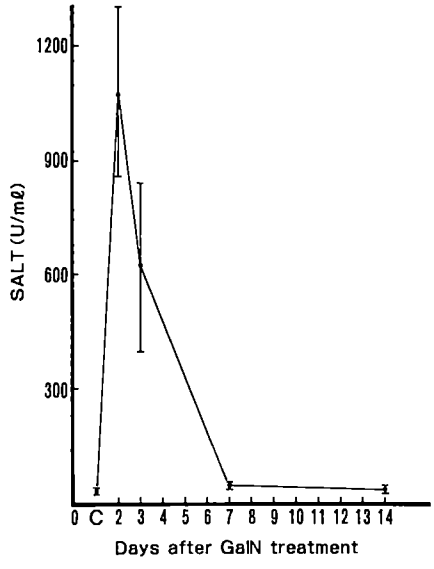

Figure 1. Changes in serum alanine aminotransferase (SALT) levels before (C) and over a period of 14 days after galactosamine treatment (n = 8, mean ± SE).

then decreased rapidly; by day 7 values returned to near normal range. If we take this variability of GalN-induced hepatotoxicity into account, rats in which SALT levels failed to exceed 200 U/ml 2 days after the treatment were not included in evaluation in experiments 2 and 3. Eight of 50 rats were excluded on this basis from analysis in experiments 2 and 3.

Experiment 2

Changes in microsomal cytochrome P-450 contents, aminopyrine N-demethylase activities, aniline hydroxylase activities, and anaerobic release of fluoride from halothane by hepatic microsomes are shown in Figure 2. Three days after the GalN treatment, all were significantly altered. It should be noted that the hepatic microsomal cytochrome P-450–dependent reactions were still significantly depressed 7 days after GalN treatment, at a time when SALT activities had returned to a near normal range. Anaerobic release of fluoride from halothane was significantly less in rats 7 days after GalN treatment than those in controls (1.36 ± 0.56 vs. 5.88 ± 0.58 nmol/mg protein, n = 6, $P < 0.001$). This was the time (7 days after the GalN treatment) chosen for experiment 3.

Experiment 3

Eight rats on the seventh day after the GalN treatment and ten saline controls were exposed to halothane anesthesia under mildly hypoxic conditions (FI_{O_2} 0.14). In saline controls, halothane anesthesia resulted in a mild but significant rise in SALT levels 32 ± 4 and 59 ± 6 U/ml, $P < 0.001$). By contrast, SALT activities were similar before and after halothane anesthesia in GalN-treated rats (45 ± 3 and 49 ± 4) as shown in Figure 3.

Discussion

It is well known that hepatotoxicity induced by a number of drugs or chemicals is dependent on their metabolic conversion to toxic metabolites (1). Halothane may have hepatotoxic potential under some circumstances. It has been postulated that halothane hepatotoxicity could be at least in part mediated by reductive metabolites of the anesthetic (2–4). We recently demonstrated that overproduction of halothane metabolites may be related to halothane hepatotoxicity in humans as well as in experimental animals (8). It is possible that decreased production of halothane metabolites as a result of an injury to the cytochrome P-450–dependent system could in turn lead to an attenuation of halothane hepatotoxicity. Indeed, it has been reported by Mazze and Baden (5) that anesthesia with halothane in oxygen did not result in superimposition of acute liver injury in already cirrhotic rats. A possible explanation for their observation may be that biotransformation of halothane to hepatotoxic intermediates is reduced in cirrhotic rats; the extent of halothane metabolism was not assessed in their study. The results of the present study indicate that halothane hepatotoxicity may be attenuated in the presence of minor acute liver injury induced by GalN in rats and that the attenuation may be related, at least in part, to a decreased hepatic biotransformation of the anesthetic. Galactosamine-induced liver injury (extensive hepatic necrosis accompanied by inflammatory infiltrates and acidophilic degeneration) is an animal model frequently used to evaluate similar types of liver injury in humans. The injury is believed to result from the metabolism of galactosamine in the liver and the consequent effect on hepatic uridine metabolism (14). The seventh day of GalN-induced liver injury was chosen because reductive metabolism of halothane was still significantly decreased, despite remarkable decrease of once elevated SALT levels.

The time course of the microsomal reductive metabolism of halothane during the GalN-induced liver injury in the present study was similar to changes in cytochrome P-450–dependent phase I reactions of hepatic microsomes. The decrease in the reductive

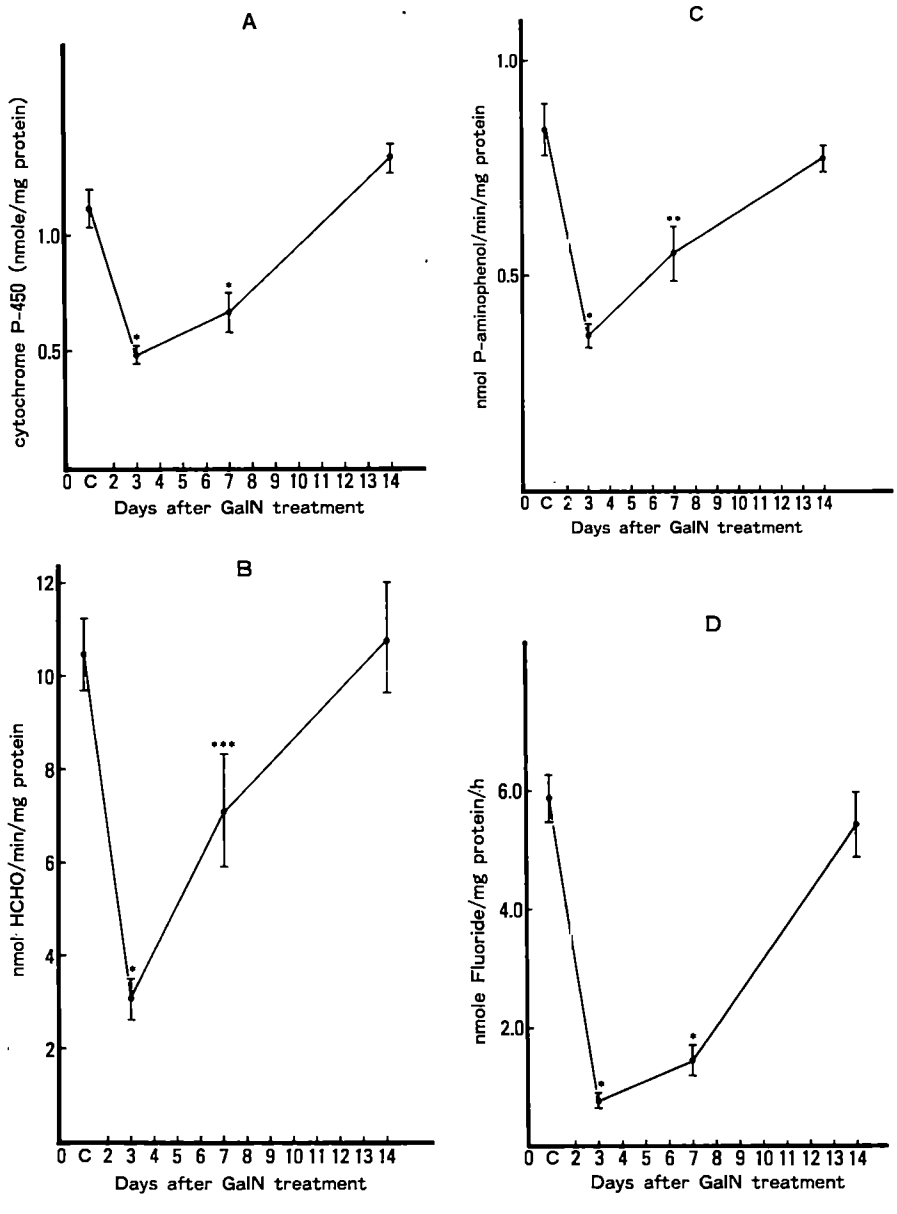

Figure 2. Changes of microsomal cytochrome P-450 contents (**A**); aminopyrine N-demethylase activity (**B**); aniline hydroxylase activity (**C**); and anaerobic release of fluoride from halothane by hepatic microsomes (**D**) during galactosamine (GalN)-induced liver injury (n = 6, mean ± SE). Aminopyrine N-demethylase activity was assessed by measuring formaldehyde (HCHO) produced during the demethylation process. Aniline hydroxylase activity was measured by following the formation of para-aminophenol from aniline. It should be noted that hepatic microsomal cytochrome P-450–dependent reactions were still significantly depressed at 7 days after GalN treatment, a time when SALT levels (Fig. 1) had returned to baseline levels. *P < 0.001, **P < 0.01, ***P < 0.05.

metabolism of halothane after GalN treatment was greater than the decrease in cytochrome P-450 contents. Although microsomal reductive metabolism of halothane is dependent on cytochrome P-450 (15), this hemeprotein is a mixture of multiple forms with different substrate specificities (16). Because it has been reported that GalN treatment leads to selective alterations of hepatic microsomal cytochrome P-450 subpopulations in rats (17), a somewhat selective destruction of a form of cytochrome P-450 involved in the reductive metabolism of halothane may in turn result in a greater decrease in the activity. The attenuation of hepatotoxicity as found in this study is in accordance with a previous report on an attenuation of fluroxene toxicity in mice pretreated with the known hepatotoxin, carbon tetrachloride (18). Because the pathogenesis of halothane-induced liver injury is a complex one and because liver injury is not fully explained by toxic metabolites alone, reduced production of toxic intermediates of halothane may not necessarily lead to an attenuation of halothane hepatotoxicity. Alternatively, it may be that the liver is regenerating after acute injury, and the failure to respond again to injury may be due to additional factors. Also, it should be borne in mind that our experiments were done under very specific conditions, conditions that were not necessarily relevant to clinical situations. However, the results of this study indicate that halothane hepatotoxicity can be attenuated in the presence of minor acute liver injury in

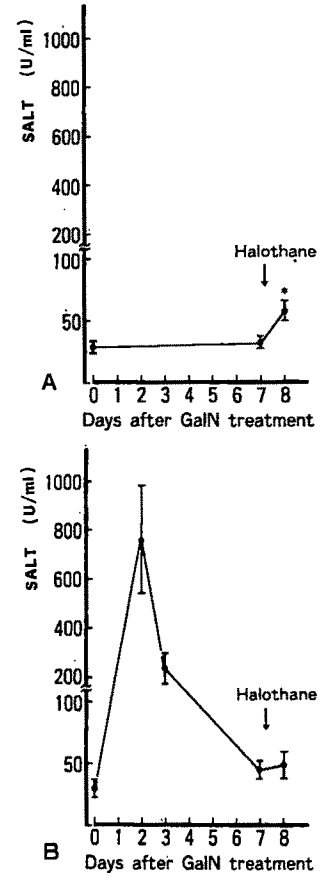

Figure 3. Effects of halothane anesthesia under mildly hypoxic conditions (FI_{O_2} 0.14) in rats 7 days after GalN treatment ($n = 8$) and in saline controls ($n = 10$). In saline controls (**A**), halothane anesthesia resulted in a mild but significant increase in SALT levels. In contrast, SALT levels were similar before and after the halothane anesthesia in GalN-treated rats (**B**). $^*P < 0.001$.

rats, and appear to support the view that halothane anesthesia is not necessarily contraindicated in subjects with impaired liver function.

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The Effect of General and Regional Anesthesia on Oxygen-Dependent Microbicidal Mechanisms of Polymorphonuclear Leukocytes in Children

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BUSONI P, SARTI A, DE MARTINO M, GRAZIANI E, SANTORO S. The effect of general and regional anesthesia on oxygen-dependent microbicidal mechanisms of polymorphonuclear leukocytes in children. Anesth Analg 1988;67:453–6.

The microbicidal activity of polymorphonuclear leukocytes (PMNL) was investigated in two groups of children undergoing hernia repair surgery. Group 1, after short general halothane anesthesia, received caudal analgesia, whereas group 2 received halothane anesthesia alone. Both groups showed a decrease in singlet oxygen production as demonstrated using chemiluminescence method. However, 24 hours after the end of surgery singlet oxygen production was fully recovered in the caudal analgesia group (group 1), whereas in the general anesthesia group (group 2), production was still significantly ($P < 0.01$) depressed. It is concluded that halothane may be associated with PMNL impairment, perhaps in a time-dependent manner.

Key Words: BLOOD, LEUKOCYTES—bactericidal activity.

Polymorphonuclear leukocytes (PMNL) play a crucial role in host defense against invading microorganisms. The microbicidal activity of PMNL depends mainly on oxidative pathways generating free oxygen radicals (e.g., superoxide anion, hydrogen peroxide, hydroxyl radical, and singlet oxygen) and, in very small quantities, on nonoxidative mechanism (e.g., lysozyme, acid lactoferin, and cationic proteins) (1–3). Commonly used anesthetics, notably halothane, have been found to have a detrimental effect on PMNL phagocytosis and microbicidal activity (4–10). These complementary functions are, however, independent and affected differently by anesthetics (11,12). In this study the effects of two different anesthetic methods on PMNL chemiluminescence in children were investigated.

Chemiluminescence (i.e., light emission) from PMNL develops during the phagocytosis-induced respiratory burst, and it depends on the presence of electronically excited states in PMNL (13). At least two mechanisms are responsible for the light emission, one involving myeloperoxidase-catalyzed reactions, the other a superoxide anion-mediated mechanism that involves the intermediate formation of singlet oxygen (14–17). Chemiluminescence is employed as a means of evaluating oxygen-dependent microbicidal mechanism in PMNL (18).

Methods

Fifteen ASA I patients (1–13 years of age, mean 7.9) undergoing elective for inguinal herniorraphy were studied. All subjects were premedicated orally with diazepam (drops) 0.3 mg/kg (not exceeding a maximum of 10 mg), 1 hour before surgery. No atropine was given.

The children were randomly classified into two groups: group 1 (caudal anesthesia, $n = 9$) and group 2 (general anesthesia, $n = 6$). Halothane 1.5% in N_2O-O_2 was, however, initially used to induce anesthesia in all patients, after which IV access was established. All subjects were monitored with an electroencephalography, automated sphygmomanometry (Dinamap), and pulse oximetry. All children

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Table 1. Chemiluminescence Values before and after Surgery in Two Groups of Children

Chemiluminescent intensity (cpm × 10^{-3})	Before induction of anesthesia	After induction of anesthesia	End of surgery	24 hours after surgery
GA*	99.0 ± 7.87†	63.3 ± 6.12	55.3 ± 10.96	76.5 ± 5.06
RB	98.5 ± 2.50	64.7 ± 3.49	66.0 ± 3.61	90.2 ± 6.59

* Abbreviations: GA, general anesthesia group; RB, regional anesthesia.
† Normal values are 98 ± 6 (mean ± SD; range, 110–85).

in group 2 were intubated after having the larynx anesthetized with a few drops of 1% lidocaine. Halothane concentration ranged from 1.5 to 2%. Children were allowed to breathe spontaneously.

Patients in group 1 received caudal anesthesia using 1% mepivacaine 0.75 ml/kg without epinephrine (19). General anesthesia was then discontinued and children were allowed to breathe room air. Additional diazepam 0.3 mg/kg, maximum 10 mg IV, was used to keep the patients asleep during surgery. In group 2 anesthesia was maintained using halothane 1.5%.

Peripheral venous samples (1 ml) were drawn into a heparinized syringe from each subject before premedication, at the end of induction of general anesthesia, immediately before intubation or caudal block, at the end of surgery, and 24 hours postoperatively.

Each patient's condition was checked postoperatively by an anesthesiologist. No child required analgesics in the postoperative period. The protocol was approved by the local ethics committee, and informed written consent was obtained from the parents of each subject.

The chemiluminescent response of PMNL was determined in 0.5 μl of the heparinized venous blood samples diluted 1:50 in calcium-free Krebs–Ringer phosphate buffer (KRP) solution (pH 7.40) containing 5.5 mM glucose (20). Chemiluminescence was produced by adding 20 μl opsonized Zymosan from *Saccharomyces cerevisiae* (Sigma Chemical Co., St. Louis, MO). Opsonized Zymosan was obtained by incubating 10 mg Zymosan and 200 μl autologous serum at 37°C for 20 minutes.

The diluted blood together with the opsonized Zymosan was incubated for 30 minutes in 910 μl KRP with luminol 10^{-3} (Sigma Chemical Co.) in dimethyl sulfoxide (DMSO, Sigma Chemical Co.). The chemiluminescence produced was quantified using a Packard luminometer 6100 Picolite and expressed as counts per minute (CPM × 10^{-3}) PMNL. The number of PMNL present in the sample studied was determined using a hemocytometer technique and by differential cell counts. Normal values were obtained from PMNL of 20 children with condition other than acute or chronic infections. Diagnoses included asthma and heart diseases.

For statistical analysis one-way analysis of variance was determined. Data are reported as mean ± SD.

Results

There were no statistical differences in age, body weight, duration of induction of anesthesia, and duration of surgery in the two groups. Samples drawn before premedication demonstrate that in all subjects chemiluminescence (in cpm × 10^{-3} cells × 1 nmol luminol) was within the normal range. Samples drawn after the induction period and before endotracheal intubation (group 2) or, alternatively, the caudal block (group 1) had chemiluminescence values significantly ($P < 0.01$) below the normal range (Table 1). At the end of surgery (approximately 45 minutes after the induction of anesthesia), all the subjects demonstrated a decrease in singlet oxygen production, i.e., chemiluminescence. In group 1 (caudal anesthesia), singlet oxygen mean production was greater than in group 2 (general anesthesia), but the difference was not statistically significant ($F = 2.34$, $P > 0.5$).

Twenty-four hours later, the singlet oxygen production in all patients in group 1 had returned to normal levels but production in group 2 subjects remained below the normal range. The difference between the two groups was highly significant ($F = 15.53$, $P < 0.01$) (Table 1).

Discussion

In the present study halothane was associated with more prolonged depression of PMNL chemiluminescence (i.e., singlet oxygen production) than was brief halothane anesthesia plus regional block. In fact, even after 24 hours the group 2 subjects (general anesthesia alone) PMNL chemiluminescence had failed to return to normal. Group 2 patients had received halothane for about 55 ± 11.7 minutes and group 1 for 7 ± 3.1 minutes.

Whether these findings have clinical significance is yet to be determined. However, the possibility that anesthesia may reduce resistance to bacterial infection was suggested by Cruse and Ford (21), who observed a greater incidence of wound infection in patients having longer periods of anesthesia and surgery than those having shorter procedures.

In in vitro studies, halothane, at clinically relevant concentration, depresses the ability of human PMNL to kill the most frequently isolated gram-negative organisms responsible for human bacteremia (*Escherichia coli* and *Klebsiella pneumonia*) (22). Halothane also depresses both oxidative and nonoxidative metabolic pathways in a dose-dependent manner (23). Chemiluminescence, or the emission of light by phagocytosing PMNL, is intimately linked to oxidative microbicidal pathways in PMNL. Therefore, the inibition in the chemiluminescence response of PMNL observed in this study was probably due to the halothane used for induction and maintenance of anesthesia. The longer reduction in chemiluminescence observed in group 2 (general anesthesia) was probably related to the longer exposure to halothane.

It has previously been reported that drugs, namely, ibuprofen (24) and corticosteroids (25), or anesthetics, such as etomidate (26), may negatively influence neutrophil metabolism. However, other possibilities exist. For example, it is well established that caudal block provides "stress-free" anesthesia in children (27,28). In contrast, cortisol plasma levels increase during surgery under general anesthesia (29), and this could be an addictional or alternative factor leading to impairment of PMNL microbicidal activity (30,31).

In this study the use of opiates postoperatively was unnecessary. Morphine and morphine-like drugs influence the PMNL microbicidal activity (32). In painful operations, use of a caudal block makes any immediate need for opiates unnecessary, and thus this technique may be helpful in avoiding further detrimental effect on the microbicidal activity of PMNL.

In conclusion, in this small series, brief general halothane anesthesia followed by caudal anesthesia with intravenous diazepam sedation reduces the duration of inhibition of PMNL microbicidal activity seen when general halothane anesthesia is used alone for lower abdominal surgery lasting approximately 45 minutes in children. Studies are in progress to confirm these findings and to establish the time course and dose-response relation between reduction in microbicidal activity of PMNL and halothane exposure.

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A Statistical Model for Pain in Patient-Controlled Analgesia and Conventional Intramuscular Opioid Regimens

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FERRANTE FM, ORAV EJ, ROCCO AG, GALLO J. A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. Anesth Analg 1988;67:457–61.

A statistical model was developed: 1) to compare the efficacy of patient-controlled analgesia (PCA) and traditional intramuscular (IM) opioids for pain relief in 40 patients after total knee replacement and, 2) to evaluate pain cycles associated with each technique. Hourly visual analog pain scores were subjected to two-way analysis of variance (ANOVA) and time-series analysis. Hourly verbal analog pain scores were used to determine predominant pain levels. According to ANOVA, PCA was no more effective than were IM opioids. Time-series analyses documented a complete cycle of pain every 5.3 hours in patients receiving IM opioids but no pain cycle with use of PCA. Analysis of PCA verbal analog scores demonstrated self-administration of opioids to "moderate" levels of pain relief with use of PCA, not to complete analgesia. These results suggest that certain patients may not envision complete postoperative analgesia as being possible. Hence, they self-administer opioids for pain relief with PCA according to their expectations. Population characteristics may modify PCA efficacy. These characteristics should be delineated and the use of PCA targeted to appropriate patients.

Key Words: ANALGESICS—narcotics. PAIN—postoperative.

The efficacy of patient-controlled analgesia (PCA) is based on the assumption that postoperative pain control is better with self-administration of opioids using small, repetitive, on-demand, intravenous doses than it is with timed, around-the-clock, IM injections. PCA is believed to be more effective than traditional IM administration because blood concentrations of opioid remain fairly constant (1–3) (Fig. 1). The analgesic effect is presumed to be constant as well, though this is not proven (4). This study presents a novel use of time-series analysis to evaluate pain cycles and the consistency of postoperative analgesia during use of PCA and traditional IM opioids. The relation between constancy of analgesia (as a function of opioid blood concentration) and clinical response (efficacy) as hypothesized for PCA (Fig. 1) is critically examined.

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Methods

This study was approved by the Committee for the Protection of Human Subjects from Research Risks. Forty patients undergoing total knee replacement were randomized into two groups (PCA or IM) after informed consent was obtained. On the afternoon before surgery, the PCA group was instructed in the use of the Abbott LifeCare PCA infuser (Abbott Laboratories, North Chicago, IL). The individual anesthetist's choice of opioid for preoperative and intraoperative use was not restricted. Patients received either regional or general anesthesia. After surgery, both groups were given IV morphine in the recovery room until they were pain-free. On arrival at the ward, IM group patients received intramuscular morphine (0.1 mg/kg) at regular 4-hour intervals. Three patients received meperidine (1 mg/kg) instead of morphine as requested by their orthopedic surgeon. PCA patients had an infuser immediately available for use. The PCA infuser was programmed to allow self-administration of 1 mg of morphine with a minimum of 10 minutes as obligatory lockout interval between consecutive doses; a maximum of 10 mg could be administered over 4 hours. Use of the PCA infuser or IM opioids was discontinued when oral

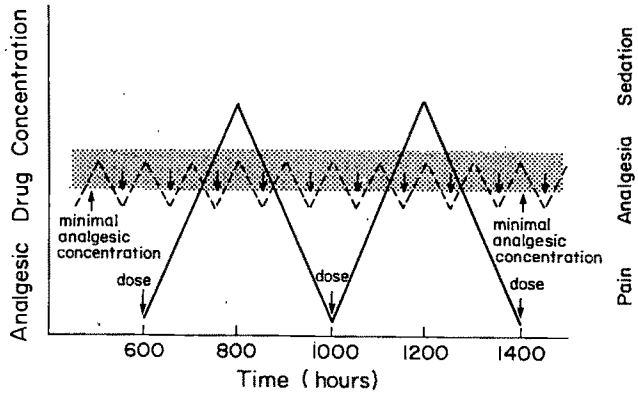

Figure 1. Theoretical relation between analgesic drug concentration, dosing interval, and clinical response for PCA (– – –) and intramuscular opioid (—). Arrows pointing downward represent administration of patient-controlled or intramuscular opioid doses.

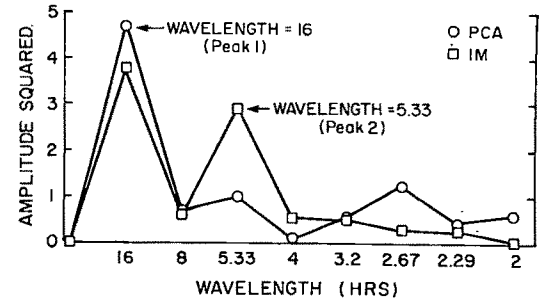

Figure 2. Normed periodograms for IM and PCA treatment groups as generated by spectral decomposition and time-series analysis of hourly visual analog pain scores. Peak 1 (wavelength = 16 hours) represents decreasing pain over time for both PCA (○) and IM (□) treatment groups. Peak 2 (wavelength = 5.33 hours) represents cyclical pain within the IM treatment group. No pain cycle is detected in the PCA group. The ordinate (amplitude squared) represents the square of the true amplitude of the waveform at the defined wavelength.

analgesics could be tolerated (after 40 hours). The total amount of opioid administered during the preoperative, intraoperative, and postoperative periods was recorded. Where appropriate, equianalgesic conversion of other opioids to morphine equivalents was performed (5).

Model for Cyclic Pain

A mixed-model analysis of variance (ANOVA) with repeated measures on individuals was used to analyze differences in the level of pain between treatment groups. Statistical analysis was restricted to measurements (visual analog scale) recorded hourly between 0600 and 2100 on the first postoperative day. Restriction of analysis to this time interval avoided sleep time. (Sleep was scored as a missing value.) Incorporation of sleep periods would have created a large and unbalanced design matrix for ANOVA. Time restriction forced alignment across circadian phase; otherwise, dampening of pain oscillations could have occurred during the averaging process.

Three main factors were included in the mixed-model ANOVA: 1) treatment (PCA versus IM); 2) hour of the day (16 levels from 0600 to 2100) and, 3) patients (numbered 1 to 40). An interaction term, treatment-by-hour, was included in the model to test for differing time trends with respect to pain between treatment groups. Treatment, hour, and treatment-by-hour were employed as fixed effects. Patient selection was considered a random effect, thereby allowing correlation between hourly recordings. Even with restriction of analysis to data obtained between 0600 and 2100, missing values during sleep caused a mild imbalance. Appropriate denominator sum of squares and degrees of freedom were therefore used to test the hypothesis of no treatment effect (6).

The second and more unique phase of the analysis involved spectral decomposition of the hourly visual analog pain scores and analysis as two time-series (7). Pain scores from each treatment group were averaged at each hour and normed periodograms were generated to detect oscillations in pain within individual treatment groups (Fig. 2). Each periodogram gives the squared amplitudes of oscillations in pain that occur with wavelengths of 2, 2.3, 2.7, 3.2, 4.0, 5.3, and 8.0 hours in respective treatment groups. The squared amplitude (ordinate in Fig. 2) represents the square of the true amplitude of the waveform at that particular wavelength. Each normalized squared amplitude behaves as a random variable from a χ^2 distribution with two degrees of freedom when there is no true oscillation in pain at a particular wavelength. A test of the null hypothesis can be made by comparing the normed periodogram value at a particular wavelength with the quantiles of a χ^2 distribution with two degrees of freedom. If the null hypothesis is rejected, a true oscillation in pain occurs at the defined wavelength.

Verbal analog pain scores were obtained hourly for 40 consecutive hours after arrival on the ward. Scores were cumulated by descriptor ("sleep," "none, mild, moderate, or severe" pain) for the individual patient and expressed as a percentage of 40 hours. Differences between treatment groups were determined by use of the Wilcoxon signed-rank test (nominal data) and Student's *t*-test (two-tailed) for "sleep" (interval data).

A questionnaire assessing the patient's evaluation of pain relief and frequency of pain was completed on exit from the study. The Wilcoxon signed-rank test or Student's *t*-test (two-tailed) were used for analysis depending on the presence of nominal or interval

Table 1. Demographic Data

	Mean age (years)	Sex		Diagnosis		
		M	F	OA*	RA	OT
PCA	68.3	8	12	14	5	1
IM	61.9	4	16	13	4	3
P Value	NS^t	NSχ	NSχ			

*Abbreviations: NS, not significant; ^{t}, two-tailed t-test; χ, χ^2; OA, osteoarthritis; RA, rheumatoid arthritis; OT, other.

Table 2. Opioid Administration*

	Preoperative/ intraoperative	Recovery room	Overall total
PCA	7.7†	17.2	59.6
IM	11.4	17.0	60.7
P Value‡	NS^t	NS^t	NS^t

†Results are expressed in milligrams of morphine.
Abbreviations as in Table 1.
*Equianalgesic conversion to morphine equivalents (mg) according to (5) where appropriate.

data. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Demographics

There were no differences in distribution of age, gender, diagnosis, or type of anesthesia between PCA and IM groups (Table 1).

Opioid Use

There was no difference in quantity of opioid administered between the two treatment groups in the preoperative, intraoperative, recovery room, and postoperative periods (Table 2).

Pain

Mean pain score (visual analog scale) in both the PCA (total observations = 274) and IM treatment groups (total observations = 260) was 3.8.

The mixed-model ANOVA showed no difference in efficacy of pain relief between PCA and IM treatment groups. There was a significant effect for hour of the day (pain was higher in early morning hours). However, there was no treatment-by-hour interaction (level of pain as a function of treatment and time of day). The total explanatory power (measure of internal consistency) of the model was $r^2 = 0.62$, which is satisfactory for biologic data of these kinds.

Time-Series Analysis

Time-series analysis showed a trend of decreasing pain over time in both treatment groups over the 16 hours analyzed (peak 1, wavelength = 16 hours, Fig. 2). There was a statistically nonsignificant oscillatory period of 5.3 hours ($P < 0.07$) detected in the IM treatment group (peak 2, wavelength = 5.3 hours, Fig. 2). No such oscillation was found in the PCA group.

Verbal Analog Pain Scores

Patients using PCA had significantly more hours of moderate pain (Fig. 3). There was no difference between the two groups in hours of mild or severe pain or hours of complete analgesia (no pain). Analysis of sleep patterns showed the incidence of sedation to be significantly greater in the IM treatment group (Fig. 3).

Patient's Subjective Evaluation of Pain Treatment Regimen

At termination of the study, patients subjectively rated PCA superior to IM opioid administration with regard to pain relief (Table 3) (despite the statistical determination of similar efficacy by examination of hourly pain scores). Patients receiving PCA also reported significantly less overall sleepiness and drowsiness, corroborating the findings of external observation. There was no difference in the frequency of pain.

Discussion

Pharmacokinetic theory holds that intramuscular administration of opioids every 3–4 hours yields widely fluctuating blood concentrations (8,9) (Fig. 1) (10). For each patient receiving parenteral opioids there is a minimum effective analgesic concentration (MEAC) representing the transition from pain to effective analgesia (8,9). However, the therapeutic window between maximum blood concentration of opioid related to severe pain and MEAC is narrow. The blood concentration–clinical effect curve is steep (8,9). For example, a change in blood meperidine concentration of as little as 0.05 μg/ml can make the difference between severe pain and analgesia (9). Sedation occurs as blood concentration increases above MEAC but with little further increase in analgesia. MEAC is

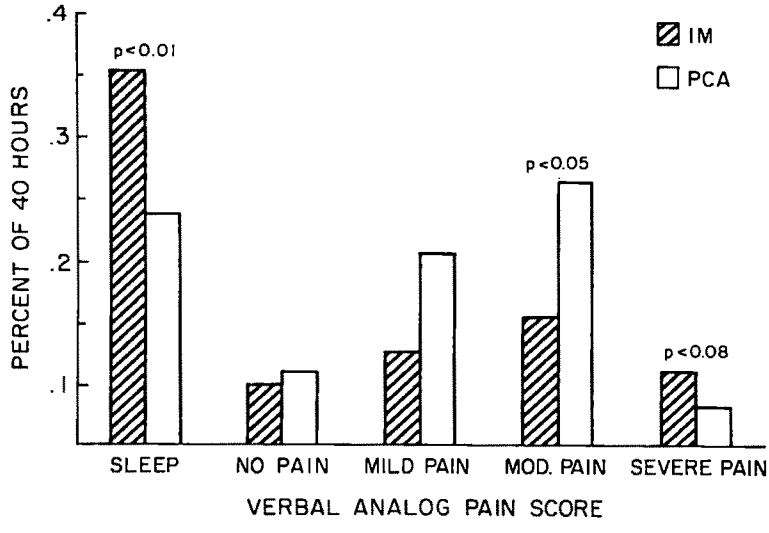

Figure 3. Mean (sleep) and median (all other) values for fraction of time spent under each verbal analog pain scale descriptor for IM and PCA treatment groups. Total observation time equals 40 hours. Abbreviation: Mod., moderate.

Table 3. Patient's Subjective Evaluation of Pain Treatment Regimen

	Subjective pain relief	Subjective frequency of pain since operation	Subjective sleepiness	Actual sleep over 40 (hours)
Scale	1–5	1–5	1–4	
PCA	3.4	2.7	1.9	10.6
IM	1.6	2.7	2.4	14.6
P Value*	$<0.05^W$	NS^W	$<0.05^W$	$<0.01^t$

Abbreviations: *, Wilcoxon signed-rank test.
Other abbreviations as in Tables 1 and 2.

associated with appreciable interpatient variability (8,9) but remains fairly constant in individual patients (10).

From the relation between opioid concentration and clinical response outlined in Figure 1, PCA would appear to be superior to intramuscular administration of opioid. With intramuscular administration, blood opioid concentrations exceed MEAC during only 35% of the dosing interval (8). PCA allows patients to self-administer opioids to achieve blood levels within a narrow range around MEAC using small, repetitive, on-demand, intravenous doses (1–3). MEAC is associated with interpatient variability but is more consistent within the individual. Allowing patients to find their own steady-state opioid blood concentration by self-administration is more logical than is administration using predetermined doses and dosing intervals.

Cyclic changes in blood opioid concentration with repeated IM administration (8,9) and steady-state concentrations with PCA have been documented (1–3). The linear relation between analgesic drug concentration and clinical effect (i.e., change in the magnitude of analgesia or pain in synchrony with the direction of change of opioid concentration) could, however, only be hypothesized (4). This paper demonstrates the validity of the theoretical relation between dosing interval, drug concentration, and clinical effect by documentation of cyclical and steady-state pain levels inherent in the use of IM and PCA techniques (Fig. 1).

The *P* value for the presence of an oscillatory period of pain of 5.3 hours in the IM group approaches statistical significance. Analysis of larger numbers of patients or refinement of experimental design would probably increase the level of statistical significance. For instance, patients in the IM group could have received placebo PCA infusers and patients in the PCA group could have received placebo IM injections. Refinement of statistical analytic technique and experimental design are presently underway.

If oscillation in pain level occurs with use of PCA, it falls below the lower limit of sensitivity of the statistical model (2 hours) as determined by frequency of data collection (hourly). Studies are underway to detect oscillatory pain at wavelengths less than 1 hour in patients using PCA.

The absence of oscillatory pain within the PCA treatment group does not represent self-administration of opioids to the point of complete analgesia, as would be expected, but to steady-state levels of "moderate" pain (Fig. 3). Analysis of verbal analog pain scores demonstrates that patients using PCA spent more hours in a moderate pain state, whereas the incidence of sedation was greater in the IM treatment group. This cannot be ascribed to inadequacy of opioid supply because only one patient receiving PCA required more than the 4-hour maximum dose limit for adequate analgesia. Based on

purely pharmacokinetic considerations, PCA should be more effective than IM injection. The higher level of moderate pain in the PCA group explains the failure of ANOVA to demonstrate a difference in efficacy of pain relief.

A possible explanation for the phenomenon of self-administration of opioids to moderate levels of pain relief may lie in the chronicity of pain in the population under study. Patients undergoing total knee replacement are usually elderly patients with chronic arthritis who have lived with a certain amount of daily pain for some time. These patients may possess certain characteristics of the psychologic construct of "learned helplessness" (11). Learned helplessness refers to a behavioral pattern characterized by emotional, motivational, and cognitive deficits in coping, associated with the belief that no effective solutions are available to ameliorate a source of stress (e.g. chronic pain). The expectations of such a population for postoperative analgesia may be different from those of a younger population with acute trauma. Despite the inability to demonstrate a difference in treatment efficacy by ANOVA and the self-administration of morphine to the point of moderate pain relief in the PCA group, patients using PCA still subjectively rated PCA as superior with regard to pain relief (Table 3). Thus, these patients self-administered opioid according to their own expectations of "possible" analgesia, not "complete" analgesia.

Therefore, the efficacy of pain relief with PCA cannot be based purely on pharmacokinetics alone as described in Figure 1. Possible modifiers of PCA efficacy (age, chronic pain, learned helplessness) may exist.

In a limited number of preliminary studies, use of PCA for postoperative pain relief has offered superior pain control with decreased opioid use (12), improvement in early mobilization (13,14), and shortened duration of hospital stay (13) compared with conventional IM therapy. Elucidation of possible modifiers of PCA efficacy will define populations for optimization of PCA use. With definition of such populations, more rapid postoperative recovery and shortened duration of hospital stay may become feasible goals for many patients.

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Continuous Infusion Epidural Analgesia in Labor:

The Effect of Adding Sufentanil to 0.125% Bupivacaine

Gareth Phillips, MB, ChB, FFARCS

PHILLIPS G. Continuous infusion epidural analgesia in labor: the effect of adding sufentanil to 0.125% bupivacaine. Anesth Analg 1988;67:462–5.

The purpose of this study was to determine if the addition of sufentanil would improve the quality of analgesia obtained with 0.125% epidural bupivacaine infusions given to women in active labor. Forty healthy laboring women were randomly assigned to two equal groups. Group 1 had epidural analgesia instituted with the bolus injection of 10–15 ml 0.125% bupivacaine containing sufentanil 2 μg/ml, followed 30 minutes later by initiation of an epidural infusion of 0.125% bupivacaine containing sufentanil 1 μg/ml at a rate of 10 ml/hr. Group 2 had epidural analgesia instituted with 10 or 15 ml of 0.25% bupivacaine with an epidural infusion of 0.125% bupivacaine begun 30 minutes later at a rate of 10 ml/hr. Infusion rates were altered as required to maintain an analgesic level to the tenth thoracic dermatome. Analgesia assessed by visual analog pain scores was significantly better in group 1. Significantly fewer epidural injections were required in group 1, and less motor weakness occurred in these patients. The addition of sufentanil to epidural bupivacaine infusions given in labor improves analgesia and reduces "top-up" requirements.

Key Words: ANESTHETIC TECHNIQUES—epidural. ANESTHESIA—obstetric.

Continuous epidural infusion techniques for analgesia in labor have advantages over intermittent epidural injections. Analgesia can be maintained continuously and the risks associated with intermittent epidural injections (intravenous injection with systemic toxicity or subarachnoid injection with total spinal) are minimized (1,2). Dilute solutions of local anesthetic are preferable for continuous infusion because total local anesthetic dose will be low, and motor block will be minimal (3).

However, a relatively large number of laboring women managed by continuous epidural infusion still require frequently repeated epidural injections both with return of pain in the first stage of labor and to provide perineal analgesia for delivery. Better-quality analgesia can be provided to women in labor by the addition of fentanyl to epidural bupivacaine infusions (4). Sufentanil is a new opioid drug with even greater lipid solubility and higher affinity for the μ-opioid receptor than fentanyl (5). These properties suggest that sufentanil may be superior to fentanyl for epidural use.

The purpose of this study was to determine if the addition of sufentanil to epidural bupivacaine infusions given to laboring women would improve the quality of analgesia obtained and whether, if this were the case, it would reduce the requirement for epidural "top-up" injections.

Methods

The subjects were 40 healthy women (American Society of Anesthesiologists Class I or II) in active labor, who were randomly classified into two equal groups. The study was approved by the institutional review board, and informed consent was obtained from the patients.

The epidural space at L2–3 or L3–4 was located by loss of resistance to air with a 17-gauge epidural needle, and an epidural catheter was advanced 3–4 cm into the epidural space. In group 1, 0.125% bupivacaine containing 2 μg/ml sufentanil was injected to institute the block. In group 2, 0.25% bupivacaine was used to commence the block. In both groups a 5-ml test dose was injected followed at 5 minutes by a further 5 ml of solution. Onset of

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analgesia was determined by visual analog pain scores (VAPS) before epidural and at 10, 20, and 30 minutes after epidural injection (6). If pain scores were greater than 30 after 20 minutes then a further 5 ml of the same solution was given.

At 30 minutes, epidural infusions were initiated in both groups of patients as follows: group 1, 10 ml/hr 0.125% bupivacaine containing sufentanil 1 μg/ml; group 2, 10 ml/hr 0.125% bupivacaine. The level of sensory analgesia was checked hourly and was maintained at the level of the tenth thoracic dermatome. If the sensory level fell the infusion rate was increased by 2 ml/hr. If the level rose the infusion rate was decreased by 2 ml/hr. Return of pain was treated by a repeat epidural injection in 5-ml increments of the following solutions: group 1, 0.125% bupivacaine with sufentanil 2 μg/ml; group 2, 0.25% bupivacaine.

Patients were assessed every hour for quality of analgesia (VAPS), level of sensory analgesia (by pinprick), blood pressure, pulse, respiratory rate, and presence of nausea, vomiting, or pruritus. Motor weakness was also assessed hourly. A modified Bromage Scale was used as follows:

0, No motor block;
1, Impaired hip flexion, normal knee and ankle movements;
2, Impaired hip and knee movements, normal ankle movements;
3, Impaired movements at hip, knee, and ankle joints.

As well as VAPS assessment of analgesia in labor, patients were also asked to assess retrospectively the quality of analgesia for delivery. The patients were interviewed when their epidural catheters were removed (less than 1 hour after delivery) and asked to grade analgesia on a four-point scale as follows:

0, No pain relief;
1, Partial pain relief;
2, Good pain relief;
3, Excellent pain relief—complete analgesia.

All of the above observations were made by nursing staff who were unaware of which drug treatments the patients were receiving.

Mode of delivery and neonatal birth weight were recorded, as were Apgar scores at 1 and 5 minutes. Neonatal respiratory rates were monitored and recorded for 3 hours after delivery to determine if neonatal respiratory depression occurred in either group.

A venous blood sample was taken from each mother before epidural placement and at the time of delivery to determine maternal plasma levels of sufentanil. A blood sample was also taken from the umbilical vein at delivery to determine fetal plasma sufentanil levels. The plasma was separated in a centrifuge and stored at −20°C until the assay could be performed. The assay was carried out by Janssen Pharmaceutica laboratories using a radioimmunoassay technique.

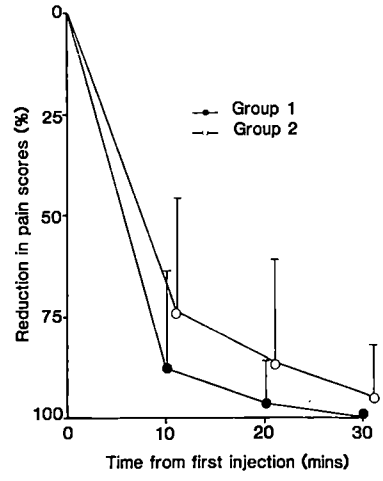

Figure 1. Percentage reduction in visual analog pain scores 10, 20, and 30 minutes after epidural injection. No significant differences exist between the two groups.

Data from the two groups were assessed using Student's t-test or χ^2 analysis with Yates correction as appropriate. $P \leq 0.05$ was considered to represent statistical significance.

Results

Patients in the two groups were of a comparable age, weight, height, and parity and had similar cervical dilation and VAPS at the time epidural analgesia was initiated.

Onset of analgesia was similar in the two groups as measured by changes in pain scores 10, 20, and 30 minutes after epidural injection (Fig. 1).

Patients given sufentanil and bupivacaine had significantly better analgesia during labor as determined by the VAPS than did patients given bupivacaine alone (Table 1).

Analgesia for delivery, assessed shortly after delivery, was also significantly better in patients given sufentanil and bupivacaine than in patients given bupivacaine only.

The mean infusion rate of analgesic solutions was significantly lower for the sufentanil/bupivacaine-treated patients (Table 2). Also, significantly more

Table 1. Quality of Analgesia for Labor and Delivery

	Group 1: bupivacaine and sufentanil	Group 2: bupivacaine
Mean VAPS in labor*	3.9 ± 9.7†	15.2 ± 13.3
Percentage reduction from initial pain score*	95 ± 10.4	80.0 ± 18.1
Analgesia for delivery		
Grade 2 (good)	3	11
Grade 3 (complete)*	16	7

*Significant difference.
†Mean ± SD.

Table 2. Bupivacaine Doses, Epidural Top-up Injections, and Infusion Rates

	Group 1	Group 2
Epidural–delivery time (hrs)	5.4 ± 2.7*	5.7 ± 2.4
Mean infusion rates of 0.125% bupivacaine (ml/hr)†	10.3 ± 0.8	11.1 ± 1.3
Repeat epidural injections		
No injections†	12	5
One repeat injection	5	11
Two repeat injections	3	2
Three or more repeat injections	0	2
Bupivacaine dose rate (mg/hr)†(infusion and top-up injections)	14.8 ± 2.0	22.3 ± 5.6

*Mean ± SD.
†Significant difference.

top-ups were required in the bupivacaine-only group, and this is reflected in the higher mean bupivacaine dose rate for group 2. The mean epidural–delivery time (the time between the first injection into the epidural space and the time the umbilical cord was clamped) was similar in the two groups. Significantly fewer patients in group 1 required a repeat epidural injection, and none required more than two repeat epidural injections. The mean total dose of sufentanil given to patients in group 1 was 78 μg (range, 40–151 μg).

Nausea and vomiting occurred equally commonly in both groups of patients, but pruritus, present in 50% of the sufentanil-treated patients, did not occur in patients given bupivacaine only (Table 3). However, the pruritus was usually only admitted to on questioning, and none of the patients requested treatment for it.

Motor weakness occurred in six patients in group 1 but was grade-1 weakness only. In group 2, 17 patients developed motor weakness and in 8 of these it was grade-2 weakness, reflecting the higher dose rate of bupivacaine and the use of 0.25% bupivacainefor repeat epidural injections. No effect of sufentanil on maternal respiratory rates was apparent (Table 4).

Table 3. Side Effects

	Group 1 (n = 20)	Group 2 (n = 20)
Pruritus*	10	0
Nausea	4	4
Vomiting	4	2
Motor weakness		
Grade 1	6	9
Grade 2*	0	8

*Significant difference.

Mode of delivery was similar in the two groups of patients, with most having a spontaneous vaginal delivery. Apgar scores were also comparable in both groups of patients (Table 5). Birth weight was similar in both groups of neonates, and respiratory rates recorded for 3 hours after delivery revealed no respiratory depression in the neonates of either group of patients. Plasma levels of sufentanil in both maternal venous blood and umbilical cord blood samples taken at delivery were too low to be detected (i.e., <0.2 ng/ml) in all 20 patients given sufentanil.

Discussion

Sufentanil was chosen for this study because it has greater lipid solubility than does fentanyl. This property permits sufentanil to pass into the lipid-rich spinal cord, leaving low drug levels in the CSF, and thus minimizing the chance of rostral spread of the drug to the vital centers in the medulla and pons (7). The higher affinity of sufentanil for the μ-opioid receptor confers on it a longer duration of action than that of fentanyl (8).

The block was commenced with 0.25% bupivacaine in patients in group 2 because personal experience has shown that 0.125% bupivacaine gives poorer results. However, 0.125% bupivacaine with sufentanil added has been shown to be equally as effective as 0.25% bupivacaine for instituting epidural sensory block and this was used in group 1 (9).

Despite the use of 0.25% bupivacaine both to initiate the block and to provide repeat epidural injections in group 2 patients, the pain scores in labor were lower in group 1 patients, in which 0.125% bupivacaine solutions were used throughout labor. The results of this study indicate an improved quality of analgesia when sufentanil is added to epidural infusions of 0.125% bupivacaine. This mixture preserves the two principal advantages of using a low-concentration bupivacaine solution: first, low total

Table 4. Maternal Respiratory Rates

		Hours after initial epidural injection				
	Control	1	2	3	4 (n = 10)	5 (n = 9)
Group 1 (bupivacaine and sufentanil)	20.9 ± 2.0*	20.7 ± 2.4	20.2 ± 2.3	20.0 ± 2.9	20.2 ± 2.6	21.1 ± 2.0
					(n = 13)	(n = 9)
Group 2 (bupivacaine)	21.2 ± 1.6	20.3 ± 1.9	20.1 ± 3.1	20.7 ± 2.4	19.9 ± 2.1	21.8 ± 2.1

*Mean ± SD.

Table 5. Fetal Condition at Birth and Respiratory Rates after Delivery

	Group 1 (n = 20) (bupivacaine and sufentanil)	Group 2 (n = 20) (bupivacaine)
Mode of delivery		
Cesarean section	1	2
Forceps	3	4
Spontaneous vaginal delivery	16	14
Apgar scores		
At 1 minute	8(6–9)*	8(6–9)
At 5 minutes	9(7–9)	9(8–10)
Birth weight (kg)	3.2 ± 0.4†	3.2 ± 0.4
Neonatal respiratory rates		
1 Hour after delivery	53 ± 9	51 ± 6
2 Hours after delivery	49 ± 10	46 ± 5
3 Hours after delivery	47 ± 6	47 ± 7

*Mean (range).
† Mean ± SD.

bupivacaine dose resulting in greater maternal safety and, second, minimal motor block. The 30% incidence of mild motor block in group 1 patients in this study is similar to that seen with 0.125% bupivacaine when given by intermittent epidural injection (10). The reliability of analgesia is improved as compared with plain bupivacaine with most women requiring no, or only one, repeat epidural injection (usually for perineal analgesia at delivery). Thus, the workload of the busy anesthesiologist is reduced. This study confirms the benefits of adding an opioid to epidural bupivacaine solutions previously reported with fentanyl (4).

The use of sufentanil, however, adds the potential problem of neonatal depression. No neonatal depression was apparent in this study as similar Apgar scores and respiratory rates after delivery occurred in the two groups of neonates. Also plasma levels of the drug in blood samples taken from a maternal vein and from the umbilical vein at delivery were too low (<0.2 ng/ml) to be detected. This suggests that neonatal depression is not likely to be a problem.

In conclusion, the addition of sufentanil to 0.125% bupivacaine epidural infusions has been shown to provide better-quality analgesia and to lower the requirement for epidural top-up injections. These benefits suggest that the combination offers significant advantages over plain bupivacaine solutions currently being used for epidural infusion.

We thank Janssen Pharmaceutica for carrying out the radioimmunoassay of plasma samples to determine plasma sufentanil levels.

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Technical Communication

Microtechnique for Quantitation of Plasma Methohexital Using Gas Chromatography and Mass Spectrometry

Kathryn J. Kestin, MD and Paul V. Fennessey, PhD

Key Words: MEASUREMENT TECHNIQUES, GAS CHROMATOGRAPHY, MASS SPECTROMETRY—barbituates. ANESTHETICS, INTRAVENOUS—methohexital.

Gas chromatographic methods to analyze methohexital concentrations have been used for the past 20 years (1,2). However, it is now possible to use highly specific and sensitive mass spectrometry as the ion detector in conjunction with high-resolution capillary gas chromatography. The major advantages of this new approach are that only small plasma sample volumes are needed (100 μl) and that, after the extraction from plasma and derivatization of the methohexital, the whole process can be automated. The basic principles described can be applied to a wide range of lipophilic drugs. For example, we have used the same techniques to assay bupivacaine and mepivacaine. The assay described in this paper was developed to investigate the pharmacokinetics of methohexital after a dose, calculated on body weight, given rectally in children (3).

Methods

Plasma stored at −70°C was thawed and 100 μl added to 2 ml of distilled water and spiked with 50 μl of an internal standard containing 1000 ng of hexobarbital in methanol. The mixture was handshaken, vortexed for 15 seconds, and then extracted twice with 4 ml of a mixture containing petroleum ether and amyl alcohol in a ratio of 100:2. (Again, the contents of the test tubes were handshaken well and vortexed for 15 seconds.) The organic solvent layers obtained from each extraction were combined in one test tube and evaporated to dryness under nitrogen at room temperature. The residue was taken up in 100 μl of the derivatizing agent BSTFA (bis-trimethylsilyl trifluoroacetamide), catalyzed with 1% TMCS (trimethylchlorosilane), and the sealed test tube heated in a sand bath at 60°C for 2 hours. The derivative obtained was diluted with 100 μl of acetonitrile and placed in a crimp-topped conical sample container compatible with the Hewlett-Packard 7672A autosampler. All glassware was silanized before use with 10% DMCS (dimethyldichlorosilane) in toluene and fixed with methanol. All reagents used were high-pressure liquid chromatography grade or better.

A Hewlett-Packard model 5790A gas chromatograph containing a 15-m DB1 capillary column and a 5970 series mass selective detector, programmed by a Hewlett-Packard 9000 series computer, was used. The oven starting temperature was 100°C; injection port, 250°C; transfer line 280°C. (The helium gas flow through the injector was constant at 95 ml/min.) The computer-programmed gas chromatograph was equilibrated for 1 minute, then ramped from 100 to 300°C at 20°C/min, and held at that final temperature for 3 minutes. This 300°C hold was used to ensure that the column was well baked so there would be no contamination carried over to subsequent samples.

Initially, complete mass spectra of methohexital and hexobarbital were obtained. A unique, abundant, high-mass ion was selected from each mass spectrum and monitored to determine concentrations of each compound (mass 239.35 in the case of methohexital and 293.45 for hexobarbital were chosen). For

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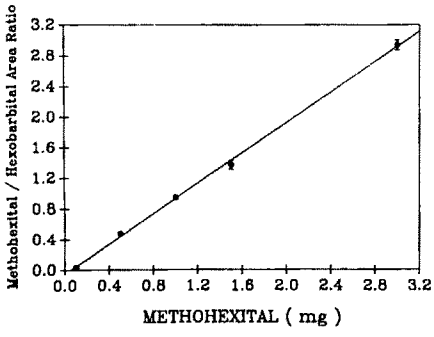

Figure 1. Methohexital standard curve. Calibration curve obtained by using a constant spike (1000 ng) of hexobarbital and various concentrations of methohexital (100–3000 ng). All points were determined in triplicate and (±1 σ) error bars are plotted on all points; however, only two are large enough to be seen.

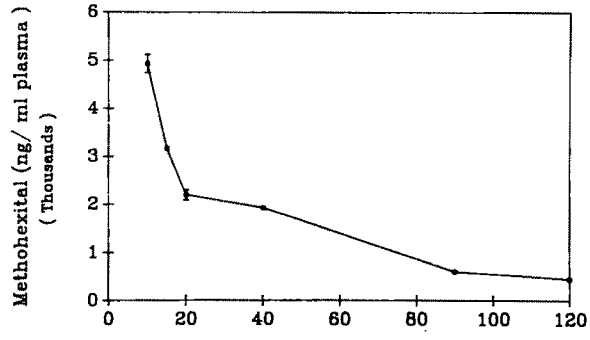

Figure 2. Rectal methohexital study. Data from one patient given 25 mg/kg 2.5% methohexital rectally (± 1 SD). After loss of consciousness, the rectal catheter was withdrawn using constant suctioning to remove as much unabsorbed methohexital as possible.

the quantitative analysis, only those two ions were selected out using a single-ion monitor program for each compound. It was thus possible to compare the relative abundance of methohexital to the known amount of internal standard (hexobarbital) added to each sample. Blank plasma samples were run to ensure that there was no background interference.

The samples in the autosampler tray were alternated with wash bottles containing acetonitrile. The computer program was designed to make three injections of each sample (3 μl per injection on the column). The data obtained (peak area and height) were automatically sorted by retention time. The total analysis time is about 3½ hours, but this includes 2 hours to derivatize the sample and does not include automated injection and data processing time. However, about 20 samples can easily be done in one batch.

Calibration graphs were prepared by adding known amounts of methohexital (range 100 to 3000 ng/ml) to 2 ml of blank plasma and adding a constant amount (1000 ng) of hexobarbital as internal standard. The samples were analyzed by the same procedure as described earlier, and the area ratio of methohexital/hexobarbital was plotted against the known concentration of methohexital. The standard curve used for this work is shown in Figure 1 and has the following parameters:

y intercept = −0.0602,
slope = 0.0010,
linear regression = 0.9995.

All the patient assays and the standard curve data points were run in sets of at least three injections to evaluate precision. If the coefficient of variation was in excess of 5%, the samples were reextracted or the gas chromatography/mass spectrometer (GC/MS) system was cleaned and a new column installed. This type of maintenance usually occurred after every 300–400 injections on the system. Actual error bars from the sets of injections are shown on both Figures 1 and 2. An accuracy check of the calibration curve was routinely made by running 100- and 1000- ng spiked plasma samples and calculating the amount of methohexital in each sample. Typical results were 97 ± 3 and 1010 ± 20 ng.

The unknown methohexital levels were calculated from the area ratios (methohexital/hexobarbital) measured by fitting the points to a regression curve using an IBM XT personal computer and Lotus 123 worksheet.

Figure 2 shows an example of the data from one child in whom the plasma methohexital values range from nearly 5000 to 440 ng/ml. Denver Children's Hospital ethics committee approved the rectal methohexital study and prior written consent was obtained from the parents. (Error bars show ±1 SD from the mean.) This patient came from a study in which anesthesia was induced in children with 25 mg/kg of a 2.5% methohexital solution administered rectally. In half the patients, after loss of consciousness, the rectal catheter was withdrawn using constant suctioning to remove as much unabasorbed methohexital as possible. The catheter in the other group was removed without suctioning. The patient in Figure 2 comes from the former group.

Discussion

The method described in this paper for measurement of methohexital concentrations was originally attempted using 2 ml of plasma, but recovery was so good that it was found that 100 μl of plasma was

sufficient for good reproducibility (coefficient of variance always <5%). This enables the measurement of methohexital levels from arterialized heel prick samples.

The standard curve shown in Figure 1 was evaluated using 100 to 3000 ng methohexital and the coefficient of variance of each point was <4%. Samples containing more than 3000 ng could also be measured after careful volumetric dilution (estimated to place the sample in the range of 100–3000 ng/ml). Using this approach, it was possible to determine the concentration of samples suspected of containing 25 $\times$ 10^6 ng/ml (25 mg/ml) of methohexital. The coefficient of variance in these cases was 6–12%.

There were peaks in both the m/z 239 and m/z 293 channels found in the blank plasma samples. However, in a patient sample such as the one shown in Figure 2, the signal-to-noise ratio was in excess of 100:1. For example, a typical methohexital peak at 90 minutes from end of infusion (low concentration) had 4×10^6 area units, whereas the blank plasma showed contamination peaks of the order of 2×10^4 area units. By using both the gas chromatographic retention time derived from authentic standards and the specific masses from methohexital (m/z 239) and the standard hexobarbital (m/z 293), we believed that the assay was specific. If there were doubts as to the source of the ion intensity in one or both of the channels, the entire mass range could be scanned to obtain a full spectrum for identification. The ability to make such spot checks is, we believe, an additional strength of this method.

The method is highly specific, searching out the one unique ion chosen, and can be used in samples contaminated with drugs or other materials. For example, some of the very concentrated samples (25 $\times$ 10^6 ng/ml) were rectal aspirates of a 2.5% methohexital solution and contained visible fecal matter. These samples, after volumetric dilution, were treated in exactly the same way as were the plasma samples.

The cost of a high-resolution capillary GC/MS is about twice that of the conventional gas chromatographs previously used. However, the GC/MS instrumentation is highly specific because it uses both the chemical separation of the gas chromatograph combined with the single-ion monitoring capability of the mass spectrometer. It is also highly sensitive, because if the assay is performed as described, it can detect 25 pg on the gas chromatograph column, which is equivalent to <1 ng/ml with a coefficient of variance of 3%. Finally, the instrumentation is versatile in that it can handle contaminated samples. By automation of the GC/MS, the time-consuming process of hand injection is eliminated. In our clinical study, we obtained, on average, eight samples per patient, each of which had a run and integration time of 20 minutes. Each sample was injected three times making an 8-hour "workload" that could be left to run overnight.

The method for detection and evaluation of methohexital levels may be extended not only to other barbiturates (e.g., thiopental) but to a wide variety of similar lipophilic drugs (e.g., bupivacaine) (4,5).

We thank members of the Department of Anesthesiology, Denver Children's Hospital, who obtained the plasma samples that we analyzed and allowed us to use their data.

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Clinical Reports

Variability of the Activated Coagulation Time

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Key Words: BLOOD, COAGULATION—activated coagulation time.

Since its introduction by Hattersley in 1966, the activated coagulation time (ACT) of whole blood has become a popular bedside test for assessing heparin-induced anticoagulation (1). Because of its simplicity and expediency, ACT has gained widespread use in cardiac and vascular surgical procedures and has had some use in hemodialysis. Many centers use ACT during cardiopulmonary bypass (CPB) procedures to ensure adequate heparin-induced anticoagulation before and during CPB, to predict the protamine dose needed to neutralize heparin, to confirm the adequacy of protamine neutralization, and to diagnose heparin rebound (2–7). Because small changes in the ACT often dictate clinical therapy with heparin or protamine, this study was designed to determine ACT variability in individual patients during cardiac surgical procedures.

Methods

After obtaining protocol approval from the institutional human studies committee, 46 patients undergoing cardiac surgical procedures requiring CPB (38 coronary artery bypass, 8 valve replacements) were studied. Each patient had two simultaneous ACT determinations at three different times during the procedure: 1) control: drawn before inducing anesthesia, 2) heparin: drawn 5 minutes after receiving an intravenous heparin bolus, and 3) protamine: 5 minutes after completing protamine infusion after CPB. Patients receiving intravenous or subcutaneous heparin within 12 hours of surgery were excluded.

ACT samples were drawn from the left radial artery at a site separated from the bloodstream by a three-way stopcock, a 15-cm segment of Gould high-pressure tubing, and a 5-cm, 20-gauge Angiocath (Becton Dickinson, Sandy, UT) catheter. To clear the sampling site of heparin flush solution, a 5-ml sample was withdrawn before taking two consecutive 2-ml ACT samples. This volume was selected to ensure an adequate discard volume to negate the 0.7-ml sampling dead space (8).

ACT samples were drawn into a 3-ml plastic syringe and a 2.0-ml aliquot of this was then transferred via an 18-gauge needle into an International Technidyne (Edison, NJ) vacuum-sealed Celite-activated ACT tube within 30 seconds. After vigorously shaking the tube, it was placed in one of four International Technidyne Hemochron chambers. Timing began as the blood sample entered the ACT tube. Each ACT tube then rotated automatically in a 37°C heat block chamber. Each tube contained a magnetic rod that remained in a dependent position until engaged by fibrin clot formation, at which time a sensor detected a change in magnetic attraction and automatically stopped the tube rotation and the timer. Experienced technicians placed the samples in the tubes and the tubes in the Hemochron device and tested these devices regularly to assure consistent 37°C heat block temperature and rotational speed.

Beef lung heparin (Upjohn, Kalamazoo, MI) doses (300 IU/kg) were administered as a bolus through the right atrial port of a pulmonary artery catheter before cannulating for CPB. After selecting protamine doses by a protamine titration method (HemoTec Hepcon,

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Table 1. Paired ACT Results with Coefficient of Variation

	Mean ± SD	Range
ACT-control (sec)	133 ± 18	93.5–198.5
ACT-heparin (sec)	526 ± 123*	292.5–887.5
ACT-protamine (sec)	122 ± 13*	95.0–153.5
CV-control (%)	3.9 ± 5.0	0–26.5
CV-heparin (%)	7.8 ± 6.9	0.2–38.1
CV-protamine (%)	3.1 ± 2.7	0–10.4

*$P < 0.05$, compared with control ACT.

Englewood, CO), protamine was infused over 5–10 minutes into the right atrium.

For each paired sample, mean and standard deviation (SD) were derived to determine the coefficient of variation (CV = 100 × SD/mean). Means and standard deviations were also calculated for the entire study population at each of the three sampling times. The mean ACTs for the heparin and post-protamine measurements were compared with the control ACT by paired *t*-tests.

Results

Table 1 shows the mean, SD, and range after averaging each ACT pairing, and the mean coefficients of variation (CV) obtained from the individual pairings. Figure 1 shows the frequency distribution of the absolute value of the difference between the two ACTS at the control, heparin, and protamine measurement periods. The CV values in Table 1 show increased within-patient ACT variability after giving heparin. Between-patient variability also increases after heparin, as judged by the range of the mean heparin ACT (Table 1). Table 2 lists statistics based on mathematical differences in the paired observations. After heparin, 40 of 46 (87%) ACT pairs differed by more than 15 seconds, whereas differences that large occurred in zero protamine and three (15%) control ACT pairs.

Discussion

The CV expresses the percentage variability of observations relative to the mean. The manufacturer's technical literature about the Hemochron device reports a CV of 4%, which presumably represents the variability of ACT values in normal individuals in the absence of anticoagulants. In the present report, each reported CV mean reflects the average of 46 CVs, each of which was derived from two observations. The CV would remain constant if the standard deviation of the paired ACT differences (Table 2) increased in proportion to the heparin-induced increase in mean ACT. The CV values indicate that ACT variability doubles after heparin doses sufficient to establish CPB.

The original manual ACT method described by Hattersley (1) may demonstrate less variability than the automated Hemochron method. However, Mabry and colleagues compared these two ACT methods and showed a closer correlation between manual and automated ACT methods after heparin-induced anticoagulation than before it (9). Their heparin doses produced lower ACT values (approximately 180–300 seconds) suitable for vascular surgery, and they did not perform paired observations with each ACT technique. Timed coagulation tests display diminished reproducibility as the clotting time prolongs (10–12). One advantage to selecting the ACT to monitor anticoagulation during cardiac surgery is that other clotting time methods (e.g., activated partial thromboplastin time, thrombin time) become either incoagulable (infinite) or highly variable at heparin concentrations below those usually required for safe CPB (10,13–15). Hemodilution and hypothermia prolong the ACT, distorting the relation between ACT and heparin concentration during CPB (16–18) and potentially complicating the diagnosis of inadequate anticoagulation during CPB. Hemodilution and hypothermia might further increase ACT variability, a possibility not investigated in the present study. After giving heparin (but before the hemodilution and hypothermia induced by CPB), the median difference between paired ACTs was 47 seconds (Table 1), with 19 of 46 (41%) pairings differing by more than 50 seconds (Fig. 1).

When using the ACT to guide clinical decisions, it would be desirable to establish an ACT value that clearly warrants supplemental heparin. Young et al. (5) used the Hemochron automated ACT method to establish the clinical safety of maintaining an ACT above 400 seconds during CPB in six children. Could ACT variability influence interpretation of Young et al.'s results? If they had averaged simultaneous paired or multiple ACT measurements, quite possibly some of their maintenance ACT values (>400 seconds by design) would have been more than 100 seconds above or below the values they observed. Consequently, it appears plausible that lesser ACT values existed and provided safe CPB anticoagulation. Young et al.'s recommended minimum ACT value (400 seconds) probably incorporates a safety margin that compensates for ACT variability. Using their recommendation, some patients would likely receive heparin doses exceeding the minimum required to

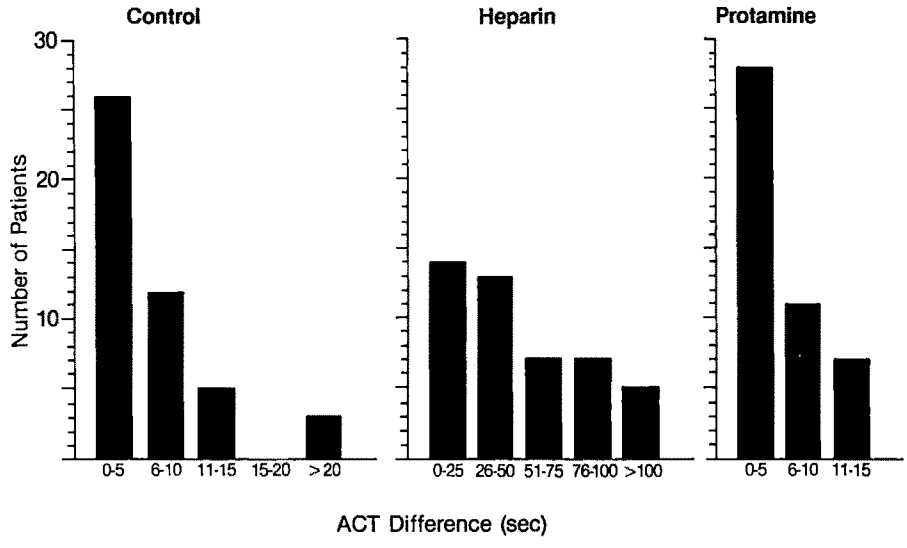

Figure 1. Frequency distribution of the observed ACT differences at the three different measurement times. Note the different numerical groupings used during heparin-induced anticoagulation.

Table 2. Difference in Paired ACT Values*

	Mean ± SD†	Median	Range
Control	7.0 ± 8.4	5	0–39
Heparin	58.7 ± 57.7	47	1–330
Protamine	5.2 ± 4.3	4	0–15

*Results are expressed in seconds.
†Mean of the absolute value of the difference (ACT1-ACT2).

prevent subclinical coagulation during CPB, but the overall effect on patient safety would be positive. Perhaps future investigations will more precisely establish a minimum safe ACT during CPB while incorporating ACT variability into this determination.

Clinicians using the CPB heparin management protocol recommended by Bull et al. (3) should be aware that post-heparin ACT variability will influence the observed ACT response to incremental heparin doses. Bull et al.'s description of the ACT vs heparin titration shows considerable variation in the obtained ACT values despite constructing a two-stage heparin dosing protocol that was mathematically designed to produce an ACT value of 480 seconds (observed ACT range, 400 to 600 seconds in 25 patients) (3). Applying the same principle to maintain an ACT between 180 and 200 seconds (or twice the control value) for vascular surgery, however, Mabry et al. (19) observed ACT values within 5% of the predicted ones. The findings in these two studies are compatible with increasing test variability as a function of mean ACT. Interpretation of the ACT response to heparin is further complicated by the possible loss of a linear dose–response relation at ACT values exceeding 600 seconds (20). The present study indicates that clinicians should expect considerable variation in single-measurement ACT responses to heparin doses even within the presumed linear portion of the dose–response relation (ACT values below 600 seconds). Routine clinical use of averaged duplicate ACT measurements would provide more consistency, but this approach seems impractical. Combining the present findings with those from previous studies (16–18,21), one might wonder whether monitoring heparin concentrations would be safer than monitoring the ACT alone. We believe that the studies of Young et al. (5) and Haddon et al. (22) validate the ACT as an independent determinant of adequate anticoagulation for CPB. The present study simply casts doubt on rigid application of minimum acceptable ACT values for CPB and precise expectations regarding ACT response to supplemental heparin doses during CPB.

ACT variability during anticoagulation could also impair the reliability of the ACT dose–response relation for determining the protamine dose for heparin neutralization. Because hemodilution and hypothermia increase the ACT for a given heparin concentration, the ACT may overestimate protamine dose requirements. Cohen (23) suggests that this CPB-induced ACT distortion diminishes over time during CPB, but his observations might have been influenced by systemic rewarming. Other investigations indicate that CPB rewarming reduces the ACT, but that the ACT prolongation at a specific heparin concentration still exceeds that observed before initiating CPB (16,22). Considering that lower protamine doses reduce postoperative bleeding (4,24), measuring blood heparin concentration (e.g., protamine titration) should predict protamine dose requirements more accurately than the ACT dose–response relation. Alternatively, averaging paired simultaneous ACT samples on resuming normothermia should

improve ACT reliability when predicting protamine doses.

When assessing the adequacy of protamine neutralization of heparin, the ACT should return to the preanesthesia control level (or less) in most instances. Average post-protamine ACT values fell significantly below preanesthesia control values (Table 1), and only 7 of 46 (15%) pairings differed by more than 10 seconds. When using the ACT to diagnose subsequent heparin rebound, an increase of 15 seconds or more would be strongly suggestive and should nearly eliminate ACT test imprecision as an explanation for the change. Factors other than heparin rebound could also contribute to an ACT increase (e.g., clotting factor deficiency, severe platelet deficit or dysfunction).

In conclusion, the ACT becomes much less reproducible in the anticoagulated state, and clinicians should allow for this when using ACT to guide therapeutic decisions. Once prolonged beyond 300 seconds, one should not expect ACT to produce pinpoint accuracy in determining heparin or protamine doses. Maintaining ACT values over 400 seconds during CPB probably constitutes safe anticoagulation. In view of ACT variability and the small number of patients investigated by Young et al. (5) and Haddon et al. (22), it appears desirable to confirm that standard with further studies.

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Combined Carotid Endarterectomy, Coronary Revascularization, and Hypernephroma Excision with Hypothermic Circulatory Arrest

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Key Words: ANESTHESIA, NEUROLOGIC—cardiovascular and urologic.
BRAIN—hypothermia and cardiovascular arrest.

Approximately 5% of renal cell carcinomas invade the inferior vena cava (IVC), forming friable, pedunculated tumor thrombus that can embolize. Fourteen to 16% of these tumor thrombi extend as far as the right atrium, in which case tricuspid valve obstruction can present an immediate threat to life (1–3). To reduce the risk of embolization during surgical manipulation and to allow complete tumor resection, the use of cardiopulmonary bypass (CPB) has been reported in patients with renal tumors (4–8). However, isolation of the affected portion of the vena cava and control of intraoperative bleeding may be difficult with conventional CPB. Therefore, CPB with total circulatory arrest has been used to provide adequate operating conditions for excision of renal tumors (9–11).

To our knowledge, however, this is the first report of the use of hypothermic circulatory arrest in a patient undergoing combined renal cell carcinoma excision, coronary revascularization, and carotid endarterectomy. The combination of these three procedures exposed this patient to cerebral ischemia, for which we used a multifaceted approach to provide cerebral protection.

Case Report

A 72-year-old, 75-kg man was admitted to the hospital for evaluation of left flank pain and exertional angina. An abdominal CT scan and vena cavograms demonstrated a right renal tumor extending through the inferior vena cava to the retrohepatic region. Cardiac catheterization revealed severe three-vessel coronary artery disease and normal left ventricular size and function. Carotid arteriograms, performed because the patient had bilateral carotid bruits, demonstrated occlusion of the right internal carotid artery and >90% stenosis of the left internal carotid artery. Combined carotid endarterectomy, coronary artery bypass grafting, and resection of the renal cell tumor were planned.

The patient had a history of moderate cigarette abuse and hypertension. His medications included metoprolol and a diuretic. Neurologic examination performed by one of the authors (DEM) on the preoperative day revealed apprehension, flat affect, moderate limitation of insight and intellectual function, and unsteady heel-to-toe gait.

The patient was premedicated with morphine sulfate 8 mg and scopolamine 0.4 mg Im, along with propranolol 20 mg orally. One hour later in the operating room, peripheral venous, radial arterial, and Swan-Ganz catheters were placed in the patient under local anesthesia. Intravenous infusions consisted of lactated Ringer's solution without dextrose. A two-channel EEG was monitored using bilateral frontotemporal leads (Neurotrac, Interspec Medical, Conshohocken, PA). Anesthesia was induced with fentanyl 2000 μg (27 μg/kg) and 100% oxygen; neuromuscular blockade was established with vecuronium 2 mg and pancuronium 8 mg. Anesthesia was maintained with fentanyl and air/oxygen, and neuromuscular blockade was maintained with pancuronium. After induction of anesthesia, blood glucose was 163 mg/dl. A two-dimensional transesophageal echocardiograph (TEE) probe (Diasonics, Salt Lake City, UT) was inserted to permit detection of segmental wall motion abnormalities and air or tumor emboli (short axis view of the left ventricle at midpapillary muscle level).

Surgery then began with an exploratory laparotomy and sampling of multiple abdominal lymph

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Table 1. Hemodynamic Changes Associated with Thiopental and Dopamine Infusions

	Pre-TPL*	During TPL	TPL and DOPA
SBP (mm Hg)	112 ± 12†	131 ± 8	110 ± 13
MAP (mm Hg)	74 ± 6	85 ± 6	70 ± 7
HR (beats/min)	56 ± 6	50 ± 5	64 ± 7
PCWP (mm Hg)	13 ± 0	12 ± 1	13 ± 6
CVP (mm Hg)	9 ± 2	8 ± 2	11 ± 2
CI ($L \cdot min^{-1} \cdot m^{-2}$)	1.9 ± 0.1	1.6 ± 0	3.3 ± 0.3
SI ($ml \cdot beat^{-1} \cdot m^{-2}$)	33 ± 3	33 ± 3	50 ± 4
SVR ($dynes \cdot sec \cdot cm^{-5}$)	1447 ± 5	2023 ± 156	774 ± 77
LVSWI ($g \cdot m \cdot m^{-2}$)	26 ± 0	34 ± 2	41 ± 8

*Abbreviations: SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; SI, stroke index; SVR, systemic vascular resistance; LVSWI, left ventricular stroke work index; TPL, thiopental; DOPA, dopamine.
†Mean ± SD.

nodes, frozen sections of which showed no tumor. Next the patient was given methylprednisolone 30 mg/kg and mannitol 25 g. Also, 2000 mg (27 mg/kg) of thiopental was given in incremental doses until the EEG was isoelectric. A 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ infusion of thiopental was then started and adjusted to maintain suppression of the EEG (1 burst/min, otherwise isoelectric) until circulatory arrest. A total of 7000 mg (93 mg/kg) of thiopental was given. During thiopental infusion, dopamine 5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was required to maintain left ventricular function until CPB (Table 1). As the thiopental was being given, surgery proceeded with a left carotid endarterectomy (CEA). When the CEA was completed, the patient's head was packed in ice and CPB was initiated. The CPB prime consisted of lactated Ringer's solution 2000 ml, sodium bicarbonate 45 mEq, heparin 5000 U, and mannitol 12.5 g. The patient was cooled to a nasal temperature of 20°C. Four distal coronary artery/saphenous vein anastomoses were performed and the distal coronary arteries were perfused with cold cardioplegic solution. An additional 4 mg of pancuronium bromide was given to prevent respiratory movement during circulatory arrest. The patient was then exsanguinated into the CPB machine, and bypass was discontinued. A cavotomy was performed and tumor thrombus was excised from the inferior vena cava. CPB was restored after 27 minutes of circulatory arrest, and the proximal coronary artery anastomoses made as the patient was rewarmed. The patient was successfully weaned from CPB after 2 hours and 48 minutes with atrial pacing, infusions of dopamine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and nitroglycerin 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intermittent doses of calcium chloride and phenylephrine, and fresh whole blood transfusions. Blood glucose was 243 mg/dl and ionized calcium was 0.85 mmol/L after CPB. Additional calcium chloride was given and anticoagulation was reversed with protamine. A right radical nephrectomy was then performed without incident to complete the surgery.

Before infusion of thiopental for suppression of the EEG, there had been no EEG evidence of cerebral ischemia. During the thiopental infusion, the echocardiogram revealed new global left ventricular hypokinesis that resolved with infusion of dopamine. There were no regional wall motion abnormalities or emboli detected with the TEE and no clinically significant EKG changes during the surgery.

The patient was transferred to the intensive care unit receiving dopamine, nitroglycerin, and phenylephrine infusions. Vasoactive infusions were subsequently discontinued, and the patient was extubated on the fourth postoperative day. The patient's MB fraction of creatine kinase increased to a maximum of 62 units/L (16% of total creatine kinase), but serial ECGs showed no evidence of infarction. Neurologic examination on the tenth postoperative day (same examiner) revealed that memory and intellectual function were unchanged, and mood, affect, and flow of conversation had improved from the preoperative state.

Discussion

Our patient had three surgically treatable lesions: renal carcinoma involving the IVC, cerebrovascular occlusive disease, and coronary occlusive disease. Once surgical intervention was accepted by the patient, the first issue was which lesion(s) should be treated. Combining tumor excision, coronary revascularization, and carotid endarterectomy was based on three considerations: 1) tumor invasion of the IVC created the constant risk of life-threatening tumor embolism; 2) the myocardial insult of circulatory arrest would be better tolerated if coronary revascularization preceded circulatory arrest; 3) and carotid endarterectomy before cardiopulmonary bypass and circulatory arrest would increase the likelihood of adequate cerebral perfusion and cooling during the periods of reduced perfusion pressure associated with CPB and hypothermia. The procedures were performed in a sequence minimizing the patient's exposure to CPB and circulatory arrest.

Brain protection was a major concern in this patient because of the global ischemia from circulatory arrest and the potential for focal ischemia from tumor, atherosclerotic plaques, and air emboli. Although hypothermia is an effective therapy for global

cerebral ischemia produced by intraoperative circulatory arrest, the optimal technique for protection from focal cerebral ischemia has not been determined (12–15). Species differences, timing of therapeutic interventions relative to ischemic insults, concurrent anesthetic administration, and conflicting results from a variety of studies make it difficult to draw conclusions regarding focal cerebral ischemia (16–24). In our patient, we chose to combine hypothermia with several of the more promising forms of therapy for focal cerebral ischemia including steroids, barbiturates, and mannitol, in an effort to avoid cerebral injury. This approach is supported by reports from clinical and experimental settings. Gisvold et al. (25) postulated that the multiple physiologic derangements of postischemic encephalopathy must be approached with multifaceted therapy. Following 18 minutes of complete global brain ischemia in pigtailed monkeys, they found that hemodilution, transient hypertension, hypothermia, pentobarbital, and dexamethasone combined in an experimental treatment protocol produced better neurologic deficit scores, overall performance categories, and histologic brain damage scores when compared to control animals. Utley and Stephens (26) report very low levels of perioperative neurological dysfunction using an approach to cardiac surgical procedures that includes a brain protection protocol consisting of hemodilution, hypothermia, thiopental, mannitol, narcotic/relaxant anesthesia, and phenytoin.

Use of the EEG as a monitor to detect cerebral ischemia requires assessment of amplitude, frequency, and symmetry of the EEG. As part of our combined therapy for focal cerebral ischemia, thiopental was given using the technique described by Nussmeier et al. (20) until the patient's EEG was supressed to one burst per minute. This degree of suppression of the EEG limited our ability to use the EEG as a monitor of cerebral perfusion. We accepted the loss of EEG activity as a monitor of cerebral perfusion because of the potential protective effect of thiopental-induced suppression of EEG activity.

Therapy aimed at preserving brain tissue is not without its own morbidity. High doses of thiopental were required in this patient to produce the desired degree of EEG suppression and to maintain it until circulatory arrest. The thiopental produced severe respiratory and circulatory depression requiring extended postoperative mechanical ventilation and infusions of vasoactive drugs. Despite this, the therapies utilized in this patient were not associated with any clinically detectable neurologic or cardiovascular complication.

The risks of cerebral injury created by this patient's multiple disease processes and the extensive surgical intervention were considerable, so we believed that the morbidity created by the anesthetic technique was justified. However, until the effectiveness of our approach is clearly established (or disproven), the associated morbidity should be balanced against the potential benefit to the patient on an individual basis.

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Anesthetic Management of a Neonate Born Prematurely with Wolff Parkinson White Syndrome

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Key Words: ANESTHESIA—pediatric.
HEART, ARRHYTHMIAS—Wolff Parkinson White syndrome.

The Wolff Parkinson White syndrome (WPW) may pose considerable problems for the anesthesiologist, because the sudden development of tachyarrythmias may result in deleterious hemodynamic changes. Preterm infants with this syndrome, especially those who weigh <1500 g, are particularly prone to tachyarrythmias (1). This may in part be associated with an underdeveloped conduction system and an immature autonomic nervous system. We describe the anesthetic management of a preterm infant with WPW syndrome, which has not previously been reported in the anesthetic literature.

Case Report

An 8-week-old male weighing 2.8 kg was admitted to the Sheffield Neonatal Surgical Unit for pyloromyotomy. He was born at 32 weeks gestation by cesarean section. When he was 5 days old, episodes of supraventricular tachycardia (SVT) occurred and an ECG confirmed the diagnosis of Wolff Parkinson White syndrome with paroxysmal SVT. The episodes of SVT became more frequent and prolonged, resulting in cardiovascular decompensation. Addition of the local anesthetic antiarrythmic drug, flecainide, to the therapeutic regimen of digoxin and propranolol resulted in better control of the tachyarrythmia. The development of pneumonia at 4 weeks required a 3-day period of intermittent positive-pressure ventilation, during which adequate gas exchange was achieved only with the aid of paralysis produced by pancuronium, the administration of which resulted in a prolonged episode of SVT (ventricular rate 280) with ensuing cardiac failure.

The tachyarrythmia responded to direct current cardioversion. The infant then progressed uneventfully with the tachycardia tolerably controlled by flecainide and propranolol. At 7 weeks he developed projectile vomiting, and a diagnosis of pyloric stenosis was made. Preoperative assessment established he had sinus rhythm, was well hydrated, and his serum electrolyte levels were normal and gastric washings had been clear for 24 hours. An ECG, arterial oxygen saturation monitor (Nellcor), precordial stethoscope, and blood pressure cuff were placed during preoxygenation. No premedication was given, and atropine was omitted from the induction sequence. After the intravenous administration of thiopental 12 mg and vecuronium 0.3 mg, the trachea was intubated with a 3.0 endotracheal tube. Anesthesia was maintained with oxygen in nitrous oxide ($F_{I_{O_2}}$: 33) and isoflurane (inspired concentration, 0–1%), and the infant was hand-ventilated, using a Jackson Rees modification of Ayre's T piece. Insertion of a radial artery catheter (24-gauge) before the commencement of surgery allowed direct blood pressure monitoring and blood gas analysis. The procedure was uneventful and 1.0 ml of bupivacaine 0.25% without epinephrine was infiltrated into the surgical wound to provide postoperative analgesia. After establishing adequate spontaneous ventilation the infant was extubated 40 minutes after the commencement of surgery and returned to the special care baby unit, where he had an uneventful recovering while being nursed in 35% oxygen with an apnea and ECG monitor for 24 hours.

Discussion

The Wolff Parkinson White syndrome is characterized by an ECG appearance of a short PR interval, a δ wave, a widened QRS, and a tendency to develop paroxysmal tachycardia. The incidence of WPW syndrome in the neonatal population is thought to be 0.1% (2). Approximately 40% of neonates with WPW syndrome have associated congenital heart disease, most commonly Ebstein's anomaly, transposition of

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the great vessels, and familial or primary myocardial disease (2). About 70% are males. The infant is particularly vulnerable in the first few months of life to the development of tachyarrythmias. This may be due to extensive postnatal structural changes beginning at birth and continuing for several months when the AV node and Bundle of His undergo shaping and molding to their final form (3). These postnatal changes may explain why the WPW syndrome occurs in infancy and later in life simply disappears (3).

A most important feature of the WPW syndrome is its association with recurrent bouts of SVT that may cause heart failure, especially in the presence of cyanotic heart disease (4). In infancy and childhood there is a frequent association between the WPW syndrome and central nervous system abnormalities, which seems likely to be due to cerebral hypoxia occurring either during bouts of tachycardia or after emboli arising from the left side of the heart of from Stokes-Adams attacks precipitating loss of consciousness and seizures (5).

The preterm infant with WPW syndrome suffering from pyloric stenosis requires careful preoperative management. It is important to continue antiarrythmic therapy throughout the perioperative period, in addition to correcting abnormalities of fluid and electrolyte balance. Digoxin and propranolol have been used extensively in children to both terminate and prevent recurrence of SVT (4). In our patient, flecainide, which slows conduction in both the specialized conducting tissues and anomalous pathways, reduced the frequency of episodes of SVT.

Successful anesthetic management of the infant with WPW syndrome is directed toward the avoidance of tachyarrythmias. Atropine should be avoided and induction of anesthesia can be safely achieved using thiopental (6), although etomidate may be more suitable (7). Vecuronium is the agent of choice to facilitate tracheal intubation, because it is free from cardiovascular side effects and its short duration of action allows spontaneous recovery of neuromuscular function without the necessity for reversal (8). Our infant had been given pancuronium at an earlier date with near disastrous consequences because of its sympathomimetic activity. Because reentry is the underlying mechanism for development of most tachyarrythmias in the WPW syndrome, any agents that slow conduction may precipitate rhythm problems. Isoflurane causes less slowing of conduction than either halothane or enflurane (9) and is the volatile agent least likely to induce a reentrant tachyarrythmia. An intraarterial catheter was utilized in this case so that, should a tachyarrythmia occur, the immediate effect on blood pressure could be assessed and samples for blood gas analysis could be conveniently taken. Fortunately SVT did not occur during our case. β-Adrenergic blockers, disopyramide, and phenylephrine (10) have all been used successfully in the intraoperative management of tachyarrythmia in adults with WPW syndrome.

The prognosis for infants with WPW syndrome depends on the frequency and severity of attacks of paroxysmal tachycardia and whether or not there is associated cardiac disease. Infants with otherwise normal hearts, who at first develop SVT when younger than 6 months of age, have the best prognosis—the bouts of tachycardia usually cease despite persistence of WPW pattern (1).

This case report suggests that thiopental, vecuronium, and isoflurane are suitable agents for the anesthetic management of infants with Wolff Parkinson White syndrome.

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Interpleural Catheter Analgesia for Pancreatic Pain

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Key Words: ANESTHETIC TECHNIQUES—interpleural catheter technique. ANESTHETICS, LOCAL—bupivacaine. PAIN—postoperative.

Reiestad and Strömskag (1) recently introduced the interpleural installation of local anesthetic solutions as a technique for the management of postoperative pain in patients undergoing cholecystectomy, renal surgery, and breast surgery. More recently Kambam et al. (2) demonstrated the efficacy of this technique in the management of postoperative pain in patients undergoing lateral and posterior thoracotomies. Our own experience with this technique substantiates these initial reports and indicates that injections of local anesthetic through an interpleural catheter are effective in abolishing both visceral and abdominal wall pain. Theoretically, then, it appears that this technique might also be useful in the management of patients with pain due to abdominal malignancies. The present case report indicates rather dramatically that such is the case.

Case Report

This 63-year-old man, first seen at the University of Illinois Pain Control Center 7 days after an exploratory laparotomy for inoperable carcinoma of the pancreas, came to us because of severe upper abdominal pain with radiation through to the back. The pain was constant and was aggravated by all but the sitting position; he was unable to assume the supine, lateral, or prone positions and, in fact, could not even stand upright. The pain was accompanied by constant nausea; and while the patient did not actually vomit, because of the nausea he had eaten nothing for the previous 3 days. For pain relief he was taking hydromorphone (Dilaudid) 2–4 mg every 2–4 hours, but each dose provided only 1 hour of pain relief.

Physical examination revealed an anxious, cachectic man in acute distress. The examination was difficult to carry out, because any attempt to change the patient's position, either actively or passively, intensified the pain. The positive physical findings were confined to the abdomen, which was extremely tender on palpation. Because of the tenderness, deep palpation was impossible, but no rebound tenderness could be elicited.

When the possible therapeutic modalities were discussed with the patient, he indicated that he was absolutely unable to participate in any procedure that would require him to assume any but the sitting position. It was considered unwise to attempt a celiac plexus block with the patient in the sitting position, not only because of the technical difficulty involved, but also because of the likelihood of hypotension following the block, especially if performed with the patient in the sitting position. Therefore, because of our recent experience with interpleural analgesia for postoperative pain, we suggested this alternative to the patient, explaining that it had not yet been tried for pain due to malignancy. Furthermore, it was pointed out that if this technique did produce relief that was not permanent, a neurolytic solution might possibly be considered subsequent to the return of his pain.

After informed consent had been obtained, a left interpleural catheter was inserted using the technique described by Reiestad and Strömskag (1) except that the procedure was performed with the patient in the sitting position. After the catheter had been taped in place, 2-ml increments of bupivacaine 0.5% were injected at 5-minute intervals. After a total of 8 ml had been administered, complete pain relief was obtained. The relief was as dramatic to the patient as to the treating physicians. The patient was suddenly able to assume any position without pain and, in fact, was ready and able to ambulate. Throughout the entire treatment period, both before and after the injection of local anesthetic, the patient's vital signs

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remained stable, and, after the onset of pain relief, neurologic examination revealed hypesthesia on the left side from T5–T12.

The patient was returned to his hospital room, where for the first time since surgery he resumed oral feedings without discomfort. The patient's pain recurred after 24 hours; and though it was much less severe, he returned to the Pain Control Center for a second injection of 8 ml bupivacaine 0.5%. This again provided complete pain relief for 12 hours; and this time when the pain returned, the patient stated that the pain was so mild that it was readily controllable with acetaminophen (Tylenol). Thus, though the option of a phenol injection had been discussed with the patient, he considered it unnecessary; and he was discharged from the hospital 72 hours after the second interpleural injection. During the 3 months after his discharge, the pain continued to be minimal and readily controllable by acetaminophen.

Discussion

Pancreatic pain, whether due to pancreatitis or carcinoma, is a problem well known to the pain specialist. Pancreatic pain, usually epigastric with radiation to the back and/or costovertebral angles, is characteristically continuous and agonizing. It is almost invariably aggravated by lying down and is relieved by sitting or standing with forward flexion. Thus, proper positioning of the patient for celiac plexus block, the technique most frequently used for relief of pain due to pancreatic carcinoma, presents a real problem. Interpleural anesthesia provides an excellent alternative in this situation. Furthermore, it may have an advantage over celiac plexus block when the tumor invades the retroperitoneal structures and the abdominal wall, because unlike celiac plexus block, the injection of a local anesthetic (and, presumably, a neurolytic agent) interpleurally provides analgesia of both somatic and visceral structures.

In our patient, postoperative incisional pain may have contributed to the patient's pain, but most of his pain had the typical distribution of pancreatic pain. Pancreatic pain is transmitted along two neural pathways: afferent fibers from the pancreas (and upper abdominal viscera) accompany the splanchnic nerves, whereas the parietal peritoneum is supplied by the intercostal nerves. Therefore, when the parietal peritoneum and the abdominal wall are involved, the lower intercostal nerves and the splanchnic nerves must be blocked. It appears that the interpleural injection of local anesthetic blocked all of these in the present case.

Although both Kuntz (3) and White and Sweet (4) found that, like the other upper abdominal viscera, the pancreas has bilateral innervation, Mallet-Guy et al. (5) consider the innervation to be predominantly left-sided. Thus, as a compromise, we elected to place a catheter in the left interpleural space first, realizing that if there was residual pain, a right interpleural catheter might be necessary as well. Fortunately, in our case the left interpleural catheter provided complete relief, so a catheter was not necessary on the right.

What is particularly remarkable in this patient is the prolonged period of pain relief (or reduction) after two injections of local anesthetic. One can only speculate that much of the patient's initial pain was due more to the inflammatory response to the tumor and the recent surgery than to invasion of the tumor and visceral distention. Thus, as is not infrequently the case with pancreatitis, interruption of the spinal reflex arc may relieve splanchnic vasoconstriction and reduce the inflammatory reaction, so that when the local anesthetic "wears off," long-lasting relief results (5).

Had we not succeeded in providing prolonged relief, we discussed with the patient the possible injection of 6% phenol into the interpleural space. Mandl (6) documented many years ago in experimental animals that although 6% phenol is capable of producing complete necrosis of the neural elements to which it is applied, when injected into the pleural space, it produces no signs of irritation or necrosis of the pleura. So while we were prepared to consider an interpleural injection of phenol, fortunately, our patient did not require this additional therapy.

In summary, we present a case that we feel demonstrates that long-lasting relief of upper abdominal cancer pain can be achieved by injections of local anesthetic through an interpleural catheter. This technique may be a good alternative to celiac plexus block in selected cases. Furthermore, if pain relief in such a case proves to be only transient, injections of dilute phenol might provide permanent relief. And finally, it is likely that this technique may be useful in the management of many or all types of pathologic pain in the upper abdomen and thorax.

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Letters to the Editor

Reversal of Flunitrazepam Amnestic Effects by Aminophylline

To the Editor:

Gurel et al. (1) have reported differential effects of aminophylline in reversal of the sedative and amnestic effects of flunitrazepam. This supports the hypothesis that there exist different mechanisms for sedative and anterograde amnestic effects of the benzodiazepines that might involve different receptors (2). We tested the ability of two benzodiazepine antagonists to reverse the sedative, psychomotor, EEG, and amnestic effects of flunitrazepam in normal volunteers (3–5), and found that all effects were equally reversed by the antagonists. Our data do not support the hypothesis that there are different receptors for the sedative and amnestic effects of benzodiazepines. According to Gurel's text, "amnesia was assessed by showing the patients five memory cards, each depicting a single object. Patients were then asked to identify each card 30, 60, and 90 minutes after an injection of saline or aminophylline." It is not clear whether at each of these times the cards were shown and later retrieved (which would be a measure of interference with acquisition of new information) or whether the patients were asked to retrieve or recognize material shown after flunitrazepam but before saline or aminophylline. The latter would not test the ability of aminophylline to reverse the amnestic effects because the material was already missed during acquisition (6). Furthermore, contrary to what is suggested, the finding that both groups of patients failed to remember the operation does not necessarily mean that aminophylline did not reverse the amnestic effects of flunitrazepam, because it was injected "when most surgical procedures were either completed or close to completion." Therefore we conclude that Gurel et al. (1) assessed the ability of aminophylline to reverse the sedative but not the amnestic effect of flunitrazepam.

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Eponymous Anesthesia Circuits

To the Editor:

I read the article by Loper et al. (1) with great interest. Although I am a proud graduate of the McGill University Medical School (Montreal, Quebec; class of 1978), we should not credit McGill University for the circuit (paragraph 3 of Methods), named for one of the great pioneers of modern day anesthesia, Sir Ivan Magill.

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Temporomandibular Joint Disease and Difficult Tracheal Intubation

To the Editor:

Like Redick (1), we recently anesthetized a patient with temporomandibular joint pathology that resulted in a difficult intubation.

A 36-year-old woman presented for removal of hardware and tenolysis in her hand. She had been told that

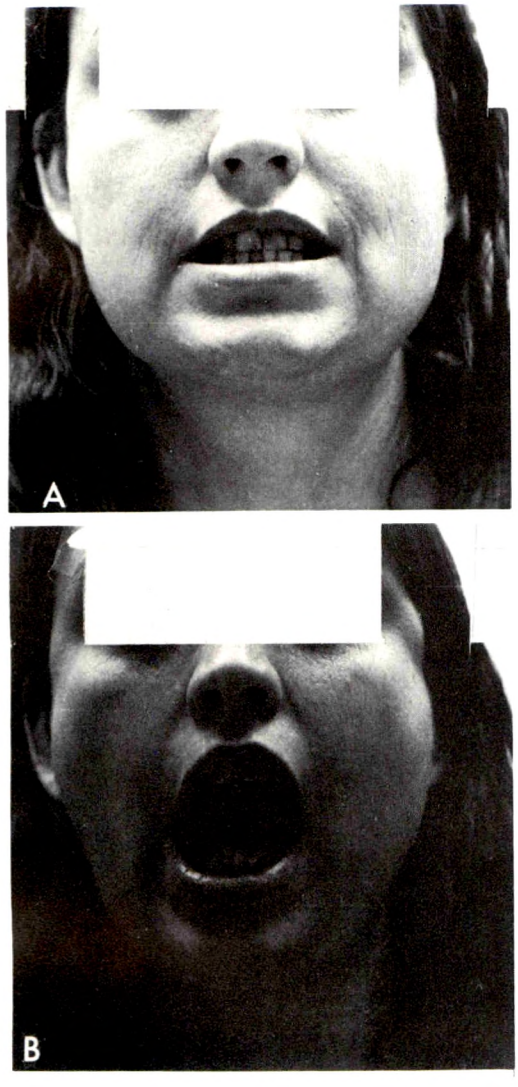

Figure 1. (**A**), Patient with mouth closed. (**B**), Patient with mouth opened showing deviation to right, the affected side.

during a previous anesthetic she had been difficult to intubate. On physical examination she could easily open her mouth and had an apparently normal airway. Review of her anesthetic records revealed that previously, after induction of anesthesia, her mouth could not be opened despite adequate muscle relaxation. She was easily ventilated by mask and was eventually intubated nasally using fiberoptic bronchoscopy. We again examined her airway and again no abnormality was appreciated. In the operating room, an axillary block was unsuccessful and we decided to use a general anesthetic. Anesthesia was induced with halothane in nitrous oxide/oxygen. The patient was easily ventilated by mask and nasally intubated by fiberoptic bronchoscopy. Her mouth could only be opened by a combination of a forward jaw thrust and rightward displacement. Oral surgical consultants found that she had a right unilateral closed lock. Postoperative examination showed that the patient opened her mouth by subtly deviating her jaw to the right (Fig. 1).

Closed lock is only one type of temporomandibular joint internal derangement. The prevalence of all temporomandibular joint derangements may be as high as 25–50% of the general population. They may present as and progress through clicking, pain, intermittent locking, limited opening and finally crepitus during opening and closing of the mouth. Patients may present with any of the above or, like ours, be totally asymptomatic. Diagnosis is by history, radiography, arthrography, and physical findings, which may be very subtle (2,3). We chose to utilize fiberoptic bronchoscopy, but in patients with unilateral closed lock a forward jaw thrust with lateral displacement of the mandible toward the affected side can permit these patients to be intubated.

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Effects of Ephedrine on Resistance and Capacitance Vessels in Humans

To the Editor:

Butterworth et al. (1), suggest that ephedrine augments venous return. This conclusion was based on experiments in anesthetized dogs having total spinal anesthesia during cardiopulmonary bypass (CPB); ephedrine increased both the mean perfusion pressure (MAP) and the reservoir volume (RV).

These results differ from our observations in five patients undergoing open heart surgery during CPB. Injection of ephedrine 30 mg into the venous reservoir of the Bentley oxygenator increased the MAP by about 30% ($P < 0.02$), but decreased rather than increased RV by about 30% ($P < 0.01$), suggesting an increase of the peripheral arterial resistance associated with venodilatation (Table 1). The increase of venous capacitance by ephedrine in humans and its decrease in the dog may be a species variation (2), or may be attributed to modification of the action of adrenergic agonists by the total spinal anesthesia induced in the dog experiments (3).

One of our patients (Patient 5, Table 1) illustrates the peripheral vascular response to ephedrine during CPB, as compared to its cardiovascular effects after termination of bypass. The patient was a 40-kg 13-year-old boy scheduled for repair of atrial septal defect (ASD). The boy had good

Table 1. Mean Arterial Blood Pressure and Cardiopulmonary Bypass Pump Reservoir Volume Before and After IV Ephedrine

	MAP		RV	
	After	Before	After	Before
Operation				
Aortic valve replacement	40	50	2700	2300
Coronary artery bypass graft	55	70	1300	800
Mitral and aortic valve replacement	85	110	500	300
Coronary artery bypass graft	80	90	500	200
Repair of atrial defect	60	95	2200	1600
Mean ± SD	64 ± 18.5	83 ± 23	1140 ± 994	1040 ± 896

Abbreviations: MAP, mean arterial blood pressure (mm Hg); RV, reservoir volume (ml).

ventricular contractility. Preoperative blood pressure was 110/70 mm Hg and ECG showed a normal sinus rhythm at a rate of 90 beats/min. He received no preoperative medication other than IM morphine 7 mg, promethazine 25 mg, and scopolamine 0.3 mg. Anesthesia was induced with midazolam 0.15 mg/kg and fentanyl 20 μg/kg followed by alcuronium 0.25 mg/kg.

After orotracheal intubation, ventilation was controlled using 100% oxygen and anesthesia was supplemented by morphine 0.5 mg/kg. The ASD was corrected during CPB using a Bentley oxygenator primed with 1500 ml Ringer's lactate solution with a pump flow of 3 L/min. After a steady perfusion was reached, ephedrine 30 mg was injected into the venous reservoir of the oxygenator; MAP increased to 95 mm Hg from 60 mm Hg, while the RV decreased to 1600 ml from 2200 ml.

After ASD repair, the aortic cross-clamp was removed and the heart was defibrillated. The patient was weaned off CPB 20 minutes after injection of ephedrine. The heart showed a normal sinus rhythm at a rate of 160 beats/min and the arterial blood pressure was markedly elevated, up to 160/110 mm Hg. The tachycardia and high blood pressure were attributed to the cardiac effects of the relatively large dose of ephedrine (0.75 mg/kg) injected 20 minutes earlier. Incremental doses of propranolol amounting to 0.6 mg were injected IV; the heart rate slowed to 100 beats/min and the blood pressure decreased to 130/80 mm Hg.

Ephedrine is a mixed β- and α-adrenergic agonist (4). Our results suggest that the vasopressor effect of ephedrine in humans may be attributed predominantly to its cardiac β-adrenergic positive inotropic and chronotropic effects on the heart, associated with a moderate α-adrenergic arteriolar vasoconstriction. These cardiovascular effects of ephedrine may explain its selection as an appropriate drug for treatment of hypotension during spinal anesthesia (5,6). Recently, a new look at sympathetic denervation during spinal anesthesia has been presented (7,8); it has been shown that the sympathetic-sensory differential after spinal anesthesia in humans averages six segments, suggesting that blockade of the cardiac accelerator fibers may be a major contributing factor in the production of spinal hypotension and bradycardia (8).

In contrast with animal experiments (1), our report suggests that ephedrine dilates the capacitance vessels in humans. Also, spinal anesthesia itself results in sympathetic blockade that produces dilation not only of the arterial and postarteriolar circulation, but also of the large veins and venules, resulting in venous pooling (5). That is why adequate fluid hydration is recommended in patients having spinal anesthesia to augment the venous return and optimize the cardiovascular response to vasopressors.

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Repeated Epidural Anesthesia for Extracorporeal Shock-Wave Lithotripsy (ESWL) Is Not Unreliable

To the Editor:

We were intrigued by the contribution of Korbon et al (1) criticizing the use of air for the loss-of-resistance test

(LORT) in continuous lumbar epidural analgesia (CLEA) for extracorporeal shock-wave lithotripsy (ESWL). They invoke the plausible explanation of release of shock-wave energy at gas-fluid interfaces (2) to postulate local tissue trauma as a cause for a high failure rate in subsequent epidural blocks. However, we believe that their data are inadequate to support their conclusions.

Information is needed on the following important determinants of success or failure of CLEA for ESWL:

1. Analgesic dosage.
2. Pain stimulus, i.e., shock-wave voltage (3); did this escalate with successive treatments?
3. Pharmacologic or anatomic causes of failure: the former is usually correctable, the latter is common in the hands of tyros and usually requires reinsertion of the needle. Thus, cyclic changes of supervisory rigor in a training program that rotates residents and non-physician personnel could be expected to produce phasic crops of anatomic failures that might have influenced results.

It is generally agreed that analgesia for ESWL requires that blockade should include the sixth thoracic dermatome (4). In our series of over 400 low thoracic and lumbar epidural blocks for ESWL, analgesia always included T6 and no failures were encountered in a sample of 42 repeat epidural blocks after previous ESWL. By contrast, Figure 2 of Korbon's paper indicates a scatter about a mean upper level of T5 with an SD of ±2.5 dermatomes for the 71 successful first cases and with an SD of ±2.7 for the group of 31 repeat cases containing 7 failures. These data imply that one or more of the 31 repeat ESWLs had an upper sensory level at T7–T8 or lower, but they do not define the precise number with inadequate dermatomal spread below T6. A substantial incidence of inadequate cephalad spread could be sufficient to explain the majority of the failures, without invoking any other factor. Application of the same analysis to the 71 first-time anesthetics indicates that 11 patients may have had sensory levels below T7–T8 and 4 or 5 of these could have been below T8. Such low levels are usually incompatible with satisfactory CLEA for renal ESWL, and we fail to understand how 100% success could have been scored in these patients.

Thus, the evidence reviewed from Korbon's series and from our own series leads us to reject the postulates that a cause-and-effect relation exists between small quantities of epidural air and subsequent failure of analgesia, and that repeated CLEA is unreliable for ESWL. Moreover, we believe that the admonition to avoid air for the LORT before ESWL is not justified by the data presented and may be medicolegally imprudent at the present time.

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In Response:

My esteemed friend, Dr. Bromage, has weathered the Saudi Arabian summer in his usual good form as evidenced by his comments on our recent article, "Repeated Epidural Anesthesia for Extracorporeal Shock-Wave Lithotripsy Is Unreliable" (1). In answer to his specific questions:

1. Analgesic supplementation was rarely given to our study patients and, when done, was in small doses. Since these data were noncontributory, we did not report them.
2. There was no trend toward increased shock-wave voltage in repeated lithotripsies. Our protocol calls for a starting voltage of 18KV for each treatment, which is then increased to 24 KV as patient comfort permits.
3. The drugs used and supervising anesthesiologists were the same for all epidurals and did not appear to contribute to the results.
4. In regard to Dr. Bromage's question as to the adequacy of the level of anesthesia (T5 ± 2.5 dermatomes as we reported), he must have misread the text. As we state in our results section, we had *no* failures with this level in either initial or repeated epidurals. All our failed (repeated) epidurals were associated with incomplete anesthesia, always below the T8 level. The failures were evident enough to necessitate another type of anesthetic before initiating lithotripsy.

Although Dr. Bromage has not witnessed in his 400 lithotripsy patients the phenomenon which we reported, we have continued to observe it frequently as our lithotripsy experience exceeds 4,500 cases. The incidence of epidural failure is about 50% for fifth and sixth time lithotripsies (n = 45 and 42, respectively) (2). Additionally, we have observed a disturbingly high incidence of neurologic complications associated with repeated epidurals for lithotripsy (1/471) (2). The fear of pathologic changes of the neuraxis is further substantiated by our animal study (3) which shows damage to the epidural and subarachnoid spaces after repeated epidurals for lithotripsy.

In summary, our large clinical experience continues to support our earlier data which has been questioned by Dr. Bromage. The clinical data increasingly suggest the possibility of epidural pathology associated with repeated epidural anesthetics for lithotripsy, a possibility further substantiated by our animal studies. Any measure that theoretically can reduce trauma to the epidural space by the lithotripter beam, such as eliminating the injection of air into the epidural space (causing little inconvenience), would seem to be a reasonable precaution.

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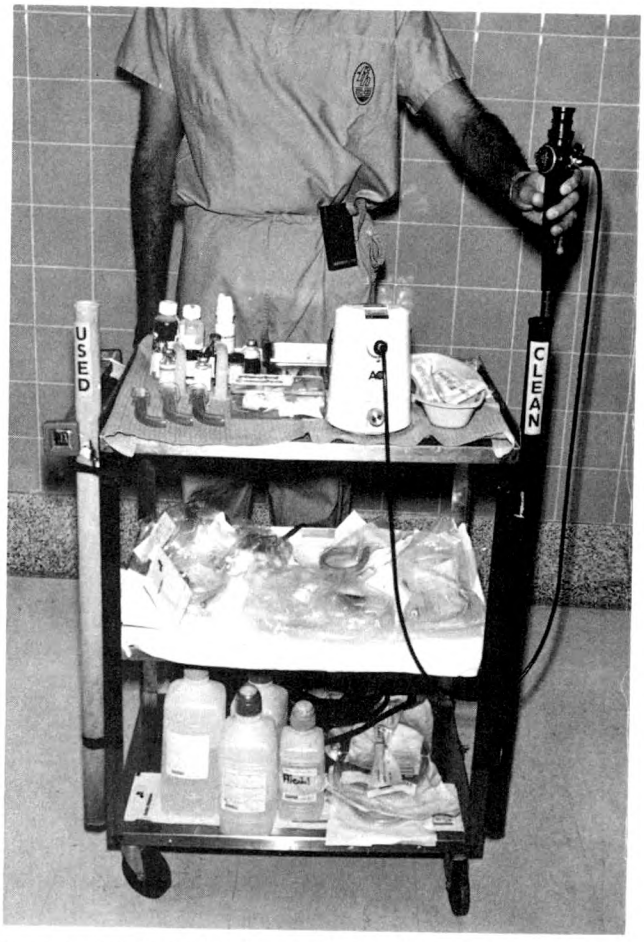

Figure 1. Labelled golf tubes attached to fiberoptic intubation cart.

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What Is Common to Both Golf and Fiberoptic Intubation?

To the Editor:

For the golfer, no matter what handicap, care of golf club grips is of prime importance. Likewise, care of fiberoptic bronchoscopes is economically and medically essential. Both goals can be achieved using the same device.

Having witnessed the damage that can occur to fiberoptic bronchoscopes after use, we devised a "cart" containing the light source, tracheal intubation accessories, and two golf club tubes (Fig. 1). The tubes cost less than a dollar and can be easily cleaned or replaced. One tube houses the clean bronchoscope ready for use. The other, clearly labelled, accepts the contaminated bronchoscope after use. With this arrangement, the bronchoscope is never bent, dropped, out of reach, or responsible for contaminating other equipment.

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Arterial to End-Tidal Carbon Dioxide Gradients

To the Editor:

In the introduction to their report on increases in arterial to end-tidal CO_2 differences after cardiopulmonary bypass, Bermudez and Lichtiger (1) make the following generalizations about these differences:

1. The magnitude of this difference usually remains stable.
2. End-tidal CO_2 tension is always lower than arterial CO_2 tension.

A review of recent literature on this subject suggests these statements may not be correct. Raemer et al. (2) studied arterial to end-tidal CO_2 differences in 15 anesthetized patients. These differences varied widely even in a given patient with stable vital signs. Two of his patients had negative arterial to end-tidal CO_2 gradients. Shankar et al. (3) have shown that these gradients were negative for 50% of women undergoing cesarean section under general anesthesia. Jones et al. (4) state that negative arterial to end-tidal CO_2 gradients may occur due to the existence of areas of the lung with long time constants and high $Paco_2$. End-tidal CO_2 may approach mixed venous CO_2 levels which exceed $Paco_2$ levels.

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To the Editor:

Bermudez and Lichtiger (1) found that the mean arterial to end-tidal Pco_2 difference ($Paco_2$–PE_{co_2}) was 6.9 mm Hg greater 30 minutes after cardiopulmonary bypass (CPB)

compared to 2 hours before CPB. The increase was seen in both smokers and nonsmokers and, curiously, $Paco_2$–PE_{CO_2} before CPB was of the same magnitude in smokers and nonsmokers.

We have found quite different changes in $Paco_2$–PE_{CO_2} associated with CPB (2). In 13 men (mean age 66 years) undergoing coronary bypass grafting, we measured $Paco_2$–PE_{CO_2} and airway, alveolar and physiologic deadspaces at four operative stages, ventilator settings being the same at the first and fourth. At the first measurement (anesthetized, before surgery), $Paco_2$–PE_{CO_2} was 6.8 ± 2.3 mm Hg; at the second stage (after sternotomy, with sternum retracted) it was 7.5 ± 3.0 mm Hg; after termination of CPB, sternum still retracted, it was 7.5 ± 2.3 mm Hg and, at the fourth measurement (after sternal closure, but still anesthetized) it was 8.3 ± 2.3 mm Hg. None of the differences between the various stages were statistically significant. We did, however, note an increase in the mean alveolar deadspace fraction from 0.32 before surgery to 0.35 after sternal closure ($P = 0.03$). We are at present expanding the material; roughly the same pattern has emerged.

How can the difference between the two studies be explained? We sampled expired gas continuously with an in-line infrared CO_2 analyzer with extremely fast response time (Servo 930) at a ventilatory frequency of 15–20 breaths/min; Bermudez and Lichtiger used sidestream sampling of gas and a mass spectrometer for measurement of CO_2. In addition, they used an expiratory pause of 4–8 seconds when sampling; this maneuver was not necessary with our system. Is it possible that sampling during a long no-flow period causes aspiration of fresh gas from the ventilator tubing?

Because there is considerable breath-to-breath variation in CO_2 elimination and PE_{CO_2}, even with automatic ventilation, we took the mean PE_{CO_2} of several breaths; it would seem Bermudez sampled only one breath. There are differences between the studies in the type of anesthesia and even in the type of patient, but it is difficult to explain the systematic increase in $Paco_2$–PE_{CO_2} in the Bermudez paper on any of the above grounds.

The methodology and discussion in the paper by Bermudez and Lichtiger raise many questions. We are not told whether the sternum was open or closed at the times of measurement, or what ventilator settings were used, although tidal volume and frequency are important determinants of $Paco_2$–PE_{CO_2} (3). Was PEEP used? We are surprised that 65-year-old smokers and nonsmokers were found to have the same preoperative group means for $Paco_2$–PE_{CO_2}. This variable is significantly greater in middle-aged smokers than in nonsmokers (4).

In the introduction, the authors state that the $Paco_2$–PE_{CO_2} difference serves as a measure of the alveolar deadspace. The relation between the two variables is complicated, being determined by the slope of the "alveolar plateau," phase III of the CO_2 single breath test, i.e., the expired CO_2 vs expired volume curve (3). Thus, it is not always true, as stated in the discussion, that "anything that increases the alveolar deadspace will increase $Paco_2$–PE_{CO_2}." For example, in our paper (2), alveolar deadspace increased significantly by the end of surgery, but so had the slope of phase III; as a result, there was no significant change in $Paco_2$–PE_{CO_2}.

Bermudez and Lichtiger speculate on pulmonary emboli as a cause of increased deadspace. But why should this occur in heparinized patients? Why should or how could emboli pass through the systemic capillaries to reach the lungs? It is more likely that the change in lung function after CPB is associated with reduced lung volume. Functional residual capacity, reduced immediately after CPB, is further reduced when the sternum is closed (5). The volume of the convective airway is also reduced by sternal closure after CPB (2) and presumably the tendency to airway closure is increased; Pao_2 is reduced, and the alveolar deadspace fraction and phase III slope are increased. These last three changes are manifestations of an increase in the spread of ventilation/perfusion ratios associated with reduced lung volume. We believe, as do Jonmarker et al. (5), that the reduction in lung volume may be caused by the retention of water as a result of hemodilution with crystalloids during CPB. In our patients (2) there was a mean increase in body fluid content of 1.8 L associated with CPB.

Interestingly, although we found a small increase in the alveolar deadspace fraction after CPB and sternal closure, the concomitant decrease in airway deadspace volume (perhaps also due to increased lung water) mitigated the effects on ventilatory efficiency; the physiologic deadspace fraction was unchanged (2). Bermudez and Lichtiger state in summary that they have demonstrated "an increased pulmonary deadspace." In fact, they have only demonstrated an increase in $Paco_2$–PE_{CO_2}. This may be associated with an increase in the alveolar deadspace, but for reasons stated above there may be no increase in physiologic deadspace.

The differences between the results of our studies and those of Bermudez and Lichtiger are important and deserve explanation. Regrettably, the lack of detail in the Bermudez paper makes this difficult. In particular, because no difference between smokers and nonsmokers was found by Bermudez and Lichtiger, validation of their end-tidal sampling method seems to be indicated.

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In Response:

Dr. Sosis' comments concerning arterial to end-tidal CO_2 tension differences are well taken. Although we cited other authors who have shown that the magnitude of this difference remains stable in hemodynamically stable anesthetized patients, we did not mean to imply that this was an absolute truism. On the contrary, we demonstrated that these differences changed significantly after cardiopulmonary bypass. The thrust of our report was to encourage anesthesiologists utilizing capnography to maintain lower levels of end-tidal CO_2 tension after cardiopulmonary bypass to achieve normocarbia.

Dr. Sosis is correct in stating that end-tidal CO_2 tension may, in certain exceptional instances, exceed the arterial CO_2 tension. Our introductory statements presented the more common clinical situation during anesthesia in which end-tidal CO_2 tension is lower than arterial CO_2 tension. As stated, this is due to the dilution of the well perfused alveolar ventilation by the deadspace ventilation. Dr. Sosis cites Shankar's study of patients undergoing cesarean section in which 50% of these paturients had negative arterial to end-tidal CO_2 tension gradients. However, because of the physiologic changes accompanying pregnancy, these patients are obvious exceptions—they tend to have greater fluctuations in their arterial CO_2 tension during the respiratory cycle due to decreased functional residual capacity and they have an increased CO_2 production. There are other interesting exceptions (e.g., exercise), but they may not be directly applicable to the stable anesthetized patient.

Fletcher et al. report different results in arterial to end-tidal CO_2 tension gradients in their study of this parameter in patients undergoing cardiopulmonary bypass. To account for this discrepancy, they propose some explanations. We acknowledge these possibilities and, in turn, wish to point out other differences in the methods employed. First, they looked at this parameter at four operative stages, whereas we examined only two (actually their second and third stages). Furthermore, their ventilator settings differed during these two stages whereas our ventilator settings were the same. In our study, each patient served as his own control and minute ventilation was adjusted so that end-tidal carbon dioxide tension was 33–36 torr. This same minute ventilation was used in the post-bypass period. PEEP was not employed.

They also comment on the fact that we found no differences in this gradient between smokers and nonsmokers. We must admit that this surprised us as well because we usually do see a larger arterial to end-tidal CO_2 tension gradient in smokers. This may be related to the small number of patients involved in this study.

There is also the difference in respiratory rate. We used a slow rate in an effort to assure sampling during the plateau (phase III) of the CO_2 tension vs time curve. If this did lead to the aspiration of fresh gas from the tubing, it is probable that this would have occurred during both sampling periods and would have little effect on our results.

As we have already stated in our response to Dr. Sosis' Letter to the Editor, the factors that determine this arterial to end-tidal gradient are complex. We sought to examine this parameter in a common clinical setting and report our findings in a simple and concise manner. Within the context of our clinical experience, we still find that this gradient is significantly increased after cardiopulmonary bypass. It has become our practice to maintain our patients at lower end-tidal carbon dioxide levels after cardiopulmonary bypass. When arterial blood gases are drawn, we find that normocarbia is maintained.

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More on Nitrous Oxide and Laser Surgery

To the Editor:

In defense of the use of 50% oxygen and 50% nitrous oxide during CO_2 laser surgery in the larynx (1), a practice challenged by Sosis (2), Hirshman et al. (3) make what we believe to be a dangerous assumption by stating: "We chose to limit the oxygen and nitrous oxide concentration *in the region of the lesion* . . . by using a cuffed endotracheal tube (emphasis added). The gas . . . in the region exposed to the laser was room air." This assumes that the sole risk of fire is from surface ignition of the endotracheal tube.

In our study (4) of the incendiary characteristics of endotracheal tubes, we found that in most cases ignition required *penetration* of the tube, which can occur with as little as 10J incident laser energy (e.g., 20W for 0.5 second). A fire then began on the inside rim of the penetration zone. This area is exposed to the gases flowing inside the tube, 50% oxygen and 50% nitrous oxide in the paper by North, et al. (1). Our experiments suggest that had the laser struck and penetrated an unprotected part of the endotracheal tube, a serious fire would probably have resulted.

We agree with Hirshman et al. (3) that an understanding of how tubes ignite is important, and although penetration of a foil-wrapped tube is unlikely, it is quite possible. Elimination of nitrous oxide, and limitation of the delivered oxygen concentration should in fact add additional safety to CO_2 laser endoscopic surgery.

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In Response:

A pair of letters in the journal (1,2) has brought to light the controversy over the use of nitrous oxide (N_2O) in the anesthetic gas mixture during laser operations on the upper airway, and we wish to share information with readers that may help clarify the issue. Sosis (1) correctly points out that N_2O supports combustion, a well documented effect (3,4), and advocates the elimination of N_2O from the anesthetic gases. On the other hand, Hirshman et al. (2) argue that a cuffed tracheal tube, wrapped in metallic tape, prevents the oxidizing atmosphere from reaching any areas exposed to the laser. Because lasers do not ignite polyvinyl chloride (PVC) in room air (3), they contend that the cuffed tubes are sufficient protection from airway fires.

We recently examined a series of 50 PVC tracheal tubes removed from patients after laser operations of the airway at our institution (5), during which patients received airway gases consisting of at least 60% helium in oxygen with a potent inhalation anesthetic (3). Of the 50 tubes, 32 were cuffed and, of those 32, 17 (53%) sustained damage to the cuff. Because PVC tubes cannot be wrapped at or below the cuff, it is not possible for metallic tape to prevent cuff damage and subsequent leakage of anesthetic gas into the operative field. Nitrous oxide can diffuse across PVC as well as across red rubber (6), and so can build up in the area where the laser is hitting, even if the cuff is intact. Furthermore, some patients with obstructive airway lesions, especially pediatric patients, do not have an airway diameter large enough to accommodate a cuffed tube; in these cases, one must use a noncuffed tube, which naturally will allow anesthetic gas to leak back to the operative site.

We therefore agree with Sosis (1) that N_2O should be eliminated from the anesthetic gas mixture whenever flammable materials are present in the airway during laser operations, and that the minimum clinically acceptable concentration of oxygen in helium be used instead.

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Carbonated Lidocaine

To the Editor:

I read with interest the article by Drs. Sukhani and Winnie on the pharmacokinetics of carbonated local anesthetics (1). However, in their discussion they discount the increase in pH from 6.5 to 6.8 as being sufficient to account for the nearly twice as fast onset of action of carbonated lidocaine vs the hydrochloride. This difference in pH, 0.3, is in fact the $\log_{10}$ of 2.

Remembering that the pK_a of lidocaine is 7.9, and with a little massaging of the Henderson-Hasselbach equation, one can show that at a pH of 6.5 lidocaine is 3.83% *un*ionized; at a pH of 6.8 the *un*ionized portion is 7.36%. This represents a 192% increase (a near doubling) in the concentration of the *un*ionized fraction (i.e., the effective dose) available to easily diffuse through tissues and membranes. Since the rate of diffusion is nearly linearly related to concentration, it does not seem so surprising that doubling the dose would reduce onset time by half. Although the other factors cited by the authors may play a role, I wonder if pH alone may be a larger factor in the more rapid onset of carbonated lidocaine than the authors indicate.

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Reference

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In Response:

Thank you for giving us the opportunity to reply to the letter from Dr. Denis L. Bourke, who disputed the statement that we made in our article, "Clinical Pharmacokinetics of Carbonated Local Anesthetics I," that the difference in pH between the two drugs is not sufficient to explain the more rapid onset produced by the lidocaine carbonate. In calculating the difference in the amount of unionized base present in the two solutions, Dr. Bourke utilizes the figure 7.9 as the pK_a of lidocaine, presumably based on the work of Rud in 1961 (1). Most authorities today indicate the pK_a of lidocaine to be 7.7 (2), a difference of 0.2, which will cause Dr. Bourke's calculations as to the amount of unionized base present at each pH to be a little low. Nonetheless, utilizing his figures and assuming them to be correct, at a pH of 6.5 if 3.83% is unionized base, because we utilized 37 cc of 1% lidocaine hydrochloride, then 14 mg of the 370 mg injected exist in the unionized form initially. Similarly, at a pH of 6.8 if the unionized portion is 7.36, then 27 mg of the 370 mg exist as the free base. Thus, although this does represent a "doubling of the dose," logic would seem to indicate that the addition of only 13 mg of local anesthetic could not reduce the onset time by half. However, logic can certainly be faulty; and to test that logic the authors recently completed a study comparing commercially prepared lido-

caine hydrochloride, lidocaine carbonate, and lidocaine hydrochloride, the pH of which had been adjusted to approximately 7.5. At this pH, approximately 38% or 141 mg of the 370 mg are available as the free base; and yet in the study just alluded to, lidocaine carbonate produced a faster onset and a greater extent of surgical anesthesia than did either the commercial lidocaine hydrochloride or the pH-adjusted lidocaine chloride. Thus we feel that our statement in the original article still stands: "The difference in pH [between lidocaine hydrochloride and lidocaine carbonate] is not sufficient to explain the more rapid onset [produced by the carbonate]."

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Book Reviews

Anesthesia for Thoracic Surgery

Jonathan L. Benumof. Philadelphia: WB Saunders, 1987, 521 pp, $75.00.

This is a 521-page treatise devoted entirely to the anesthetic management of noncardiac thoracic surgery. Initial inspection shows that it has a uniform style from beginning to end, as would be expected for a single-authored work. The chapters follow a logical sequence with new topics referring to previously laid foundations. Each chapter begins with an outline and includes multiple figures and tables to emphasize or synthesize important points. These are so generously placed that it is possible to cover a chapter or topic quickly by following these aids referring to the text only when greater depth is desired. The organization is straightforward so that finding material on a given topic is easy. The five major sections are basic considerations, preoperative considerations, intraoperative considerations for all thoracic surgery, intraopertaive considerations for special thoracic surgery, and postoperative considerations.

The section on basic considerations reviews background material, including a history of thoracic surgery and the development of suitable anesthesia. The points emphasized are the stumbling blocks that held back progress and the solutions that have become a part of current practice. The anatomy and physiology of the respiratory system are covered next in sufficient detail to allow one to follow the normal processes and appreciate how disruption through disease or intervention affects outcome. Finally an entire chapter is devoted to the physiology of the open chest and lateral decutibus position because these are pivotal to the material of this text.

Preoperative considerations comprise two main topics. First is the evaluation of both surgical and chronic disease processes. Specific emphasis is placed on examination and testing, particularly in determining suitability for surgery and implications for anesthesia. Next is a section on preoperative treatment including rationale, methods, and expected benefits.

Intraoperative considerations, the focus of this work, includes two chapters covering over one-half of the book. All aspects of management, from monitoring to anesthetic choices to problems of double-lumen tubes and one-lung ventilation, are covered in detail. Particularly refreshing is the logical treatment of these issues. The author avoids blanket recommendations and discussions of his practice and instead develops rational indications for each intervention. His treatment of issues in one-lung ventilation alone is reason enough to have this text.

Last, the section on postoperative considerations includes likely complications and their management, with a major emphasis on respiratory management. Of special importance is the final chapter on pain management. This has become an important area for anesthesiologists since treatment by nerve block or epidural opioids have become routine in many centers.

From beginning to end this is a well done book. Thoracic anesthesia has become an area with highly specialized techniques. Positioning of double-lumen tubes, ventilatory maneuvers to treat hypoxia during one-lung ventilation, and ventilatory techniques for bronchial surgery are just some of the areas where rapid development has taken place over the last 15 years. Much of the material is scattered in reviews, symposia, letters, reports, and articles. The value of this book is in its logical synthesis of these advances. The author puts these developments in the perspective of experience. This book is destined to be one of the classics, a source to be reviewed when the topic of thoracic anesthesia is discussed.

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Handbook for the Academic Physician

W. C. McGaghie, J. J. Frey, eds., New York: Springer-Verlag, 1987, 398 pp, $49.50.

The eager new recruit to academia quickly learns that his or her clinical training, no matter how fine, is insufficient preparation for the diverse roles of the academic physician. Donning the professorial white coat, one is expected to be a teacher, clinical researcher, writer, and participant in innumerable organizational activities, among other less well-defined roles. Recognizing this paradox, this book presents course materials used at the University of North Carolina during the past 6 years in a faculty fellowship program the goal of which has been to equip physicians with the basic knowledge and skills needed for academic success. As noted in the foreword, "These skills are *not* bells and whistles. They are the elements of academic life

that make the position truly academic." The clinical focus of the 22 contributors, almost all from North Carolina, is family medicine, but the material is applicable to all medical specialties, including anesthesiology.

The book has five sections, the first of which discusses professional development: the academic medical center and the new recruit's relationships in it, planning and developing a viable academic career, managing academic committees, and participating in external organizations. An education section describes curriculum development, teaching methods, and the evaluation of both students and programs. More than a third of the book offers guidance in the planning, conduct, and support of clinical research. A section on professional communications offers similar help with written, oral, and visual presentation of one's work. The final section is a timely one on medical ethics and how they can be taught.

Although much of this information is found elsewhere, and often in greater detail, it is presented here in a compact format that is well honed, easily read, and practically oriented. The text is supplemented by many line drawings and tables. The references are carefully chosen; each section also has a brief annotated list of suggested reading.

Some of the most interesting material is in the especially insightful early chapters that dissect the academic physician's role from a sociomanagerial perspective. We are reminded that the academic physician has remarkable autonomy in an unusually disorganized environment; he juggles multiple hats, but the reward system is not closely aligned to the tasks and his performance. With research funding declining, he becomes increasingly dependent on clinical revenues (also declining), threatening his scholarly performance and leading to conflict and stress. Noting that the academic physician's role is inherently divisive, one chapter is devoted to work-related stress that probably underlies much of the familiar "professional burnout" that claims so many young faculty after only a few years. Suggestions are provided on how he (and his chairman) can address role ambiguity, conflict of expectations, and professional overload.

This book should be read by newcomers to academic medicine, but older faculty may also find much of value here.

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Third Report of the Victorial Consultative Council on Anaesthetic Mortality and Morbidity 1985

John D. Paull and George D. Robinson, eds. Health Department Victoria, Melbourne, Australia

This 34-page publication is a collection of case reports of morbidity and mortality associated with anesthesia administered in the state of Victoria, Australia. There are reports on 37 mortalities and 21 serious morbidities, voluntarily reported by medical practitioners to the Victorial Consultative Council on Anaesthetic Mortality and Morbidity in 1985. Inquiry at the state level into anesthesia-associated morbidity is unique in Australia, and it is probably unique at any level of any government agency. After each reported case has been reviewed by the Council, a confidential letter is sent to the reporting doctor with the Council's conclusions. It is hoped that this feedback will encourage further reporting. Furthermore, the Council uses these cases to illustrate important points of anesthetic technique that may be of value to other practitioners, hopefully "helping them to avoid the traps and pitfalls into which it is so easy to fall." Because reporting is voluntary, the information cannot be used to determine rates of adverse events or for other statistical purposes.

Some of the cases did not involve anesthetic or surgical error, e.g., atropine-resistant bradycardia, anaphylactic reactions, or intraoperative embolism. Those cases in which error was involved ran the gamut from errors that fulfill the Peter Principle (injection of thiopentone into an epidural catheter) to those in which the most talented practitioners of our speciality might be found lacking—e.g., death during emergency cesarean section resulting from primary pulmonary hypertension. Illustrated are the adverse outcomes resulting from inadequate preoperative assessment, inadequate preoperative resuscitation, failure to monitor appropriately—intraoperatively and postoperatively—failure to communicate with the surgeon, reversal of central oxygen and nitrous oxide lines, nonavailability of monitors, and failure to transfer patients to a higher level facility.

The report is readable and brief. It is written in a conciliatory, nonjudgemental, understated style. It is humbling! Reading about individual cases sensitizes us to our own vulnerabilities and the dangers that we may present to our patients more effectively than does a comprehensive, systematic, methodologically sound survey of morbidity and mortality. The Council has thus performed the worthy service of helping us "to avoid the traps and pitfalls. . . ."

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Brain Injury and Protection During Heart Surgery

Hilberman, M. ed. Boston: Martinus Nijhoff Publishing, 1988, 173 pp, $58.50.

The occurrence of a neurologic disaster during cardiac surgery is a major concern to all who care for these patients. Out of these concerns, patterns of patient care evolved, often based on misunderstanding, dogma, incomplete data, and the "latest series of 2 or less." This volume summarizes, in a logical and thorough fashion, an enormous amount of factual information concerning the mechanisms, incidence, and prevention of neurologic complica-

tions during cardiopulmonary bypass. The physiology of cerebral blood flow is discussed in two comprehensive and understandable chapters, one of which is devoted exclusively to acid-base, CO_2 and temperature correction. The "low-flow, low-pressure" technique for bypass is presented in another chapter supported by appropriate physiologic rationale. Embolization is discussed in two more chapters, and the risks and problems of macro- and microembolization are clearly differentiated. Methods for assessing neurologic function are presented, including psychometric, biochemical, electrophysiologic, and clinical approaches. Finally, the problems of hypothermic circulatory arrest are considered both as the unique entities that they are and also in conjunction with our understanding of the pathophysiology of cerebral injury. Although one might quibble at the absence of a discussion of combined carotid/cardiac procedures, the overall impression is that of a thoroughly researched and well done volume. It may not be required reading for every anesthesiologist, but for those who provide anesthesia during cardiopulmonary bypass, it is a welcome addition to the library.

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Practical Neuroanesthesia. Anesthesia Clinics of North America

Frost EAM, ed. Philadelphia: WB Saunders, 1987, 230 pp, $25.95 single issue, $60.00 for four issues.

This brief, clinically oriented text covers some aspects of neurosurgical anesthesia. The authors are primarily from Albert Einstein College of Medicine, and the discussions may reflect institutional practices. Chapters include "anesthetic monitoring during neurosurgery," "fluid and the electrolyte management in neurosurgical patients," and "choice of neuroanesthetic technique." In addition, there are discussions of endocrine abnormalities, pediatric neuroanesthesia, central nervous system trauma, anesthesia for spinal surgery and peripheral nerve surgery, chronic pain treatment, and postanesthetic care (with a separate chapter on nutrition). Some of the material, for example, nutrition, has not been covered in other neuroanesthesia textbooks.

The book has many good points. It has a reasonably detailed discussion on fluid and electrolyte management in neurosurgical patients (a topic that is ignored in most textbooks). There is a nice introduction to neurosurgical interventions for chronic pain problems. Finally, there is a most engaging chapter by Victor Marrow on "decision making: case studies from ethical and legal perspectives." This chapter, I thought, is an excellent introduction to what is becoming an increasingly important issue for physicians, patients, and their families. For those unfamiliar with this area, Dr. Marrow's chapter would be a good start.

This book, however, is not a complete handbook or textbook of neuroanesthesia. For example, there is very little on anesthetic approaches for patients with cerebral vascular disease such as aneurysms. I could find no discussion about the use of muscle relaxants during neurosurgery. In particular, the possibility that succinylcholine might increase intracranial pressure was not discussed. There are some statements with which one might take issue. For example, on page 538 the author suggests that the hazards of nitrous oxide in neurosurgical anesthesia outweigh its benefits and that few neuroanesthesia centers continue to use nitrous oxide. With respect to currency and completeness of references, in the chapter "choice of neuroanesthesia technique," the classic work of Hunter on intravenous barbiturate anesthesia was missing. In addition, there were no references to readily available papers on the effects of potent narcotics on cerebral blood flow and metabolism.

For those who subscribe to Anesthesiology Clinics of North America, this volume is a reasonable contribution to that series. For others, there are similarly priced textbooks that may provide a more balanced and complete introduction to the area of neurosurgical anesthesia.

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Errata

Miller BR, Friesen RH. Oral Atropine Premedication in Infants Attenuates Cardiovascular Depression during Halothane Anesthesia. Vol. 67, No. 2., February 1988, p. 180.

The authors would like to change the address for correspondence to: Dr. Miller, Keesler Medical Center, SGHSA, Keesler Air Force Base, MS 39534.

Anderson JA, Kafer ER. Evaluation of the Accuracy of Four Pulse Oximeters during Outpatient Dental Anesthesia (abst). Vol. 67, No. 2S, 1988 Supplement, p. S2.

The authors wish to inform readers that in the "Methods" section, the sentence that begins, "A second blood sample was obtained. . ." should go on as follows: "after 2 minutes. General anesthesia was induced using methohexital (1–1.5 mg/kg) and maintained with intermittent boluses of 10–30 mg as needed." Also, in line 3 of the second paragraph under "Discussion," change "$y = 1.21 \times -19.1$" to read "$y = 1.03 \times -2.33$."

Schwartz N, Eisenkraft JB. Preventing Kinking of Small Endotracheal Tubes (letter). Vol. 67, No. 3, March 1988, p. 297.

The authors wish to inform readers that paragraph #2 should read as follows:

2. The standard 2.5-mm ID Portex tube is 15 cm in length, whereas the 3.5-mm tube is 19.5 cm. Shortening the 3.5-mm tube by 4 cm, as described by Yamashita and Motokawa (1), would result in similar lengths for both tubes! These technical difficulties may be resolved by employing a 4.0-mm ID, 21-cm length, outer tube that has been shortened by 10 cm.

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Anesthesia and Analgesia

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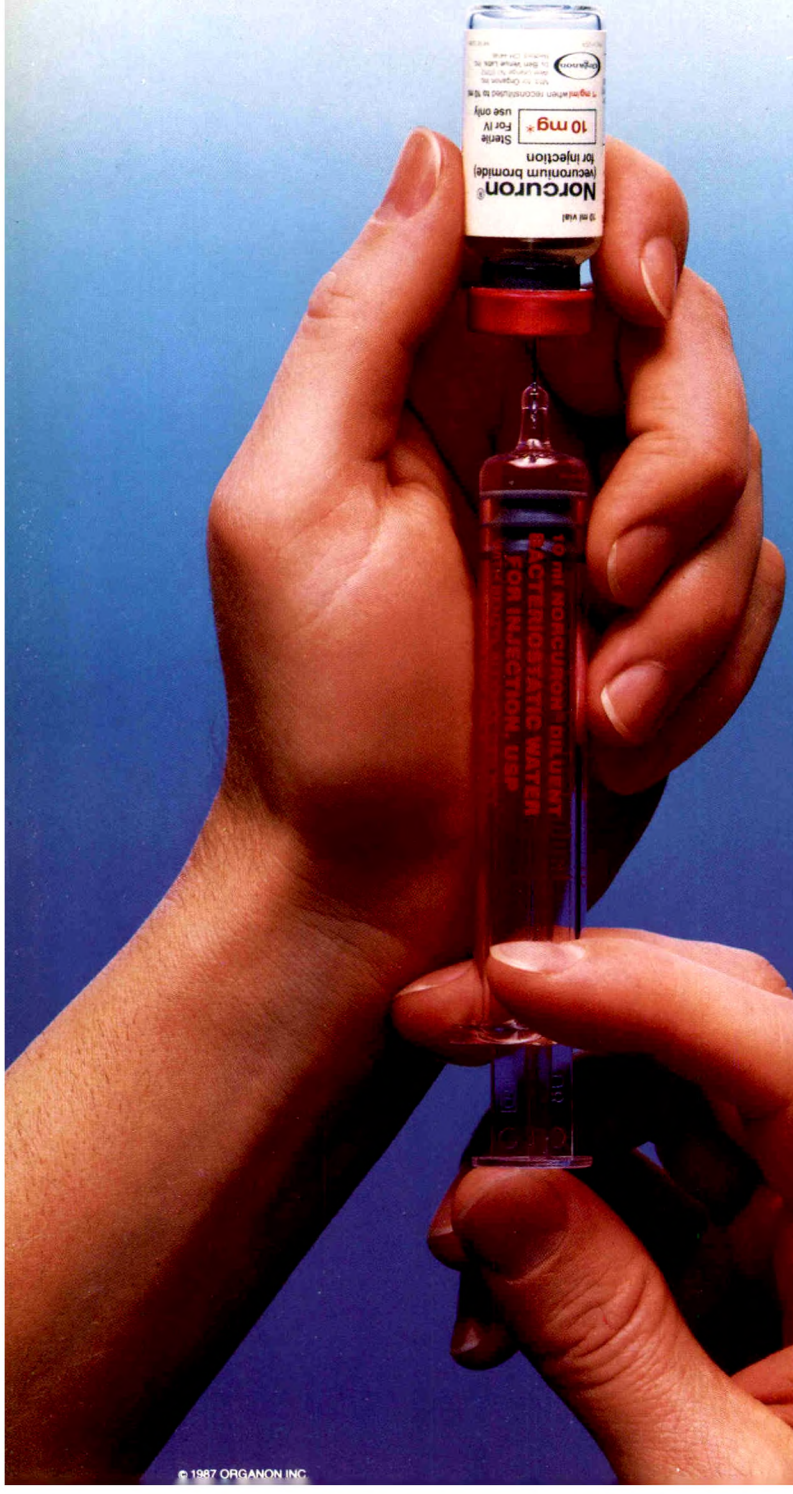

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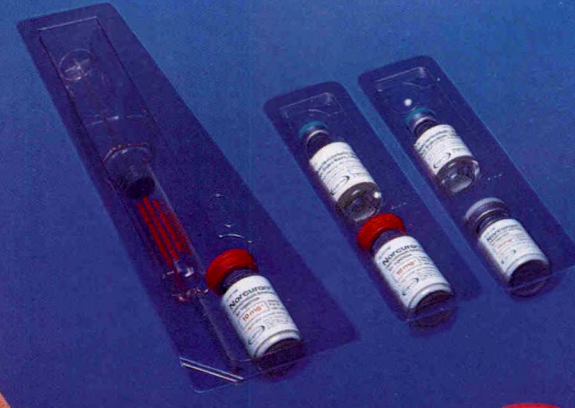

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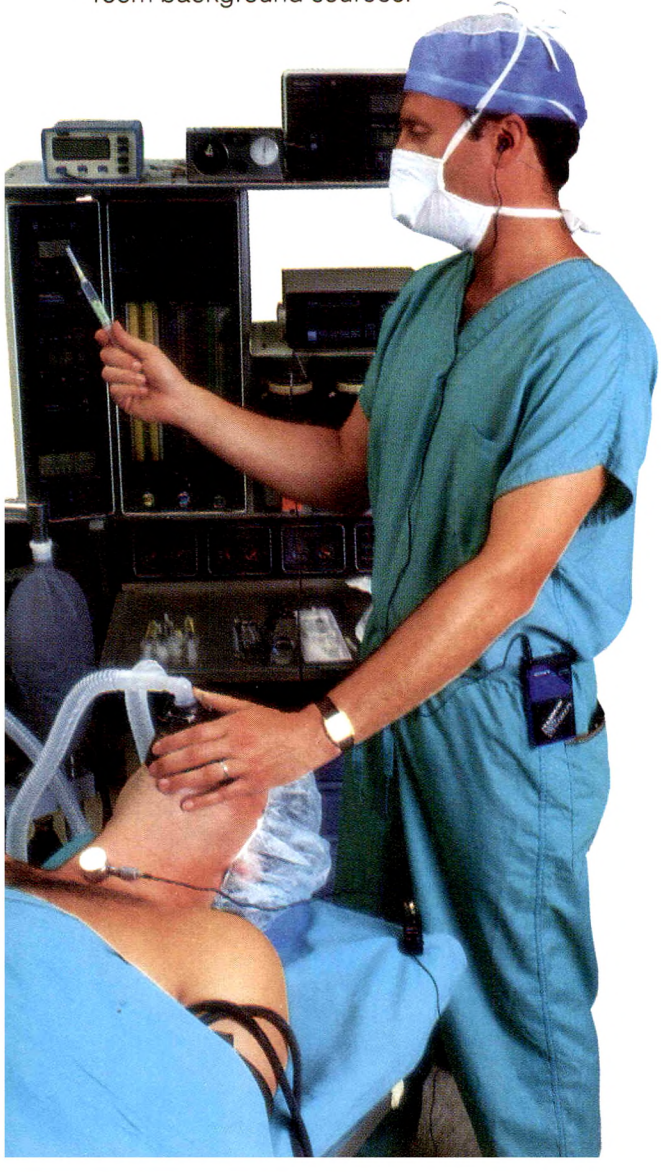

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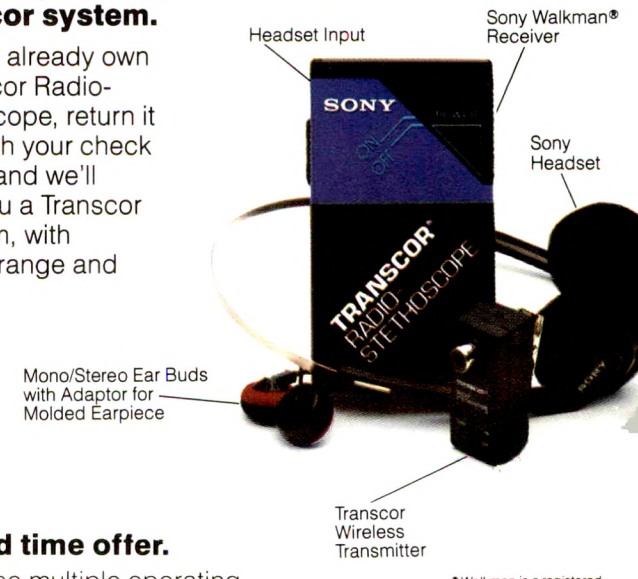

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Contents

Volume 67, Number 6, June 1988

SCIENTIFIC ARTICLES


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Mivacurium Chloride (BW B1090U)-Induced Neuromuscular Blockade During Nitrous Oxide–Isoflurane and Nitrous Oxide—Narcotic Anesthesia in Adult Surgical Patients

Stanley Weber, MD, Barbara W. Brandom, MD, Danae M. Powers, MD, Joel B. Sarner, MD, Susan K. Woelfel, MD, D. Ryan Cook, MD, Vicki J. Foster, MSPH, Barbara F. McNulty, MPH, and J. Neal Weakly, PhD

WEBER S, BRANDOM BW, POWERS DM, SARNER JB, WOELFEL SK, COOK DR, FOSTER VJ, McNULTY BF, WEAKLY JN. Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide–isoflurane and nitrous oxide–narcotic anesthesia in adult surgical patients. Anesth Analg 1988; 67:495–9.

The neuromuscular and cardiovascular effects of mivacurium were studied in 90 adult patients during nitrous oxide–oxygen–isoflurane (n = 45, ISO group) and nitrous oxide–oxygen–narcotic (n = 45, BAL group) anesthesia. Neuromuscular blockade was measured using electromyographic activity of the adductor pollicis muscle after supramaximal stimulation of the ulnar nerve at 2 Hz for 2 seconds at 10-second intervals. To estimate dose–response relations, three subgroups of nine patients in the ISO group received mivacurium doses of 0.025, 0.03, and 0.04 mg/kg, respectively. Similarly, three subgroups of nine patients in the BAL group received mivacurium doses of 0.03, 0.04, and 0.05 mg/kg, respectively. The ED_{50} and ED_{95} of mivacurium in each group were estimated from linear regression plots of log dose vs probit of maximum percentage depression of neuromuscular function. The estimated ED_{50} values for the ISO and BAL groups were 0.029 and 0.041 mg/kg, respectively. The estimated ED_{95} values for the ISO and BAL groups were 0.045 and 0.058 mg/kg, respectively. Recovery indexes were measured in 26 patients who received ED_{95} or greater doses of mivacurium in either the ISO or BAL groups. The recovery index was shorter in the BAL group (5.5 ± 1.6 minutes [n = 10]), than in the ISO group (7.4 ± 3.0 minutes [n = 16]). The addition of isoflurane (0.5–0.75% end-tidal concentration) to nitrous oxide–narcotic anesthesia augments the degree of neuromuscular blockade from a given dose of mivacurium and also prolongs the recovery index.

Key Words: NEUROMUSCULAR RELAXANTS—mivacurium.

Mivacurium (BW B1090U), a nondepolarizing neuromuscular blocking agent with a short duration of action, is metabolized by human plasma cholinesterase (1). This agent has undergone clinical trials to evaluate its neuromuscular and cardiovascular effects and has been found to be effective and safe (2–4). We compared the dose–response relation for mivacurium, the onset time, and the duration of neuromuscular blockade during nitrous oxide–isoflurane and nitrous oxide–thiopental–fentanyl anesthesia.

Methods

Ninety patients (ASA status I–II) of either sex, 18–67 years old, having low- to moderate-risk elective surgical procedures requiring tracheal intubation were studied. Women of childbearing potential were excluded. Their mean age was 33.8 ± 11.5 years (19–57) (mean ± SD [range]); their mean weight was 68.4 ± 16.4 kg (45–100); and their mean body surface area was 1.8 ± 0.3 m^2 (1.3–2.3). The study was approved by the Biomedical Institutional Review Board of the University of Pittsburgh and of Allegheny General Hospital; informed consent was obtained from all

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Received from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; the Division of Anesthesiology, Allegheny General Hospital, Pittsburgh, Pennsylvania; and the Division of Clinical Research, Burroughs Wellcome Company, Research Triangle Park, North Carolina. Accepted for publication January 18, 1988.

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patients. No patients received aminoglycoside antibiotics or antihistamines within 48 hours of the study. Patients were premedicated with morphine (0.05–0.15 mg/kg) and/or diazepam (0.1–0.2 mg/kg) or midazolam (0.02–0.06 mg/kg) IM. Plasma was obtained for pseudocholinesterase enzyme activity and dibucaine number measurements.

Anesthesia was induced intravenously with thiopental (4–10 mg/kg) and fentanyl (2–10 μg/kg). Tracheal intubation was facilitated with intratracheal lidocaine spray (4%, 4 ml). Anesthesia was maintained in 45 patients with nitrous oxide (70%), oxygen (30%), and isoflurane (0.5–0.75% end-tidal concentration) (ISO group). In the other 45 patients (BAL group), anesthesia was maintained with nitrous oxide (70%), oxygen (30%), and fentanyl (4–10 μg/kg) Ventilation was controlled to maintain end-tidal CO_2 between 35 and 40 mm Hg. Temperature was maintained in the normal range.

The ulnar nerve was stimulated supramaximally with repetitive trains-of-four stimuli (2 Hz for 2 seconds at 10-second intervals) using surface electrodes on the forearm. The compound electromyogram (EMG) of thumb adduction (adductor pollicis) was recorded using a Puritan-Bennett/Datex Monitor (5,6). The amplitude of the first (T1) of the train-of-four response was used to quantify the degree of neuromuscular block; the amplitude of the T1 response after administration of mivacurium was expressed as a percentage of the control (baseline) T1 response.

After a stable baseline EMG height was obtained, a bolus dose of mivacurium (0.03 mg/kg IV), estimated to be the ED_{25}, was administered to a subgroup of patients (n = 9) for each anesthetic background. All relaxant doses were injected rapidly (over 5–10 seconds) through a T-connector into a rapid IV infusion. Two additional subgroups of nine adults for each anesthetic background received an initial bolus of mivacurium selected to approximate the ED_{50} and ED_{75}. These subsequent doses were estimated from a log-dose probit response curve for each anesthetic that was updated after each subgroup was studied. The maximum percentage neuromuscular blockade from each single dose of mivacurium was transformed to a probit value; the dose (mg/kg) was transformed to log dose. Composite linear dose–response curves were determined for each anesthetic using calculation by the method of least squares (7). The ED_{50} and ED_{95} of mivacurium during narcotic and isoflurane anesthesia were estimated from the linear regression equations using estimates of the ED_{25}, ED_{50}, and ED_{75}. Dose–response relations were calculated using both the dose expressed in milligrams per kilogram and in milligrams per square meter. The slope and intercept of the regression line for mivacurium dose–effect during isoflurane anesthesia was compared to that for narcotic anesthesia using a *t*-test (8).

Bolus doses of mivacurium approximately one and two times the estimated ED_{95} were administered to subgroups of nine patients in each of the two anesthetic groups. Mean arterial pressure (MAP) and heart rate (HR) were noted at baseline and 1, 2, 3, and 5 minutes after the initial bolus dose. Differences in MAP and HR were assessed with a repeated measures analysis of variance.

The time to maximum blockade, maximum blockade, and the times for neuromuscular transmission to return to 5% (T5), 25% (T25), 50% (T50), 75% (T75), and 95% (T95) after the initial injection of mivacurium were noted. The recovery index (T25–T75) was calculated from these data. Recovery was referenced to final baseline (maximum T1 obtained).

Summary data are reported as means ± SD. Differences were considered statistically significant if $P \leq 0.05$.

Results

Two patients were excluded in the calculation of dose–response curves because of subnormal pseudocholinesterase activity and dibucaine number. Two other patients receiving 0.15 mg/kg mivacurium also had subnormal dibucaine number or low pseudocholinesterase activity. Data from these four patients are presented in Table 1. Another patient with very prolonged effect was found to have subclinical myositis. These five patients were deleted from calculations of neuromuscular effect.

During nitrous oxide–narcotic anesthesia, the neuromuscular blockade achieved with mivacurium (0.30 mg/kg) was 13 ± 19% (0–55) (mean ± SD, [range]); with 0.40 mg/kg was 57 ± 35% (6–90); and with 0.50 mg/kg was 72 ± 20% (32–96). The neuromuscular blockade achieved during nitrous oxide–isoflurane anesthesia with mivacurium (0.025 mg/kg) was 40 ± 32% (12–94); with 0.030 mg/kg was 44 ± 30% (8–98); and with 0.040 mg/kg was 82 ± 14% (52–100). Dose–response relations were determined for each group (n = 26 per group) and are presented in Table 2. There was no significant difference between the slopes of the two dose–response relations assessed by two-tailed *t*-test, and as evidenced by the similarity of the ratios of ED_{95}/ED_{50} for each anesthetic group. The intercepts of the curves are different: the isoflurane curve is shifted to the left of that for narcotic anes-

Table 1. Data from Patients with Abnormal Pseudocholinesterase Activity or Dibucaine Number

	Patient no.			
	1	2	3	4
Pseudocholinesterase activity (U/L)*	2750	1910	1210	590
Dibucaine number (%)†	32	84	66	58
Dose (mg/kg)	0.150	0.150	0.030	0.030
Anesthetic background	BAL	ISO	BAL	ISO
Maximum blockade (%)	100	100	100	98
T25 (min)	11.8	35.2	16.8	5.6
T25–T75 (min)	7.2	4.2	5.9	5.6

*Normal range (2436–4872).
†Normal range 70–95% inhibition.

Table 2. Dose–Response Relations of Mivacurium in Adults

	n	ED_{50} (mg/kg)	ED_{95} (mg/kg)	R	ED_{50} (mg/m^2)	ED_{95} (mg/m^2)	R
Anesthetic							
Balanced (BAL)	26	0.041	0.058	0.68	0.017	0.025	0.62
Isoflurane (ISO)	26	0.029	0.045	0.57	0.011	0.019	0.44

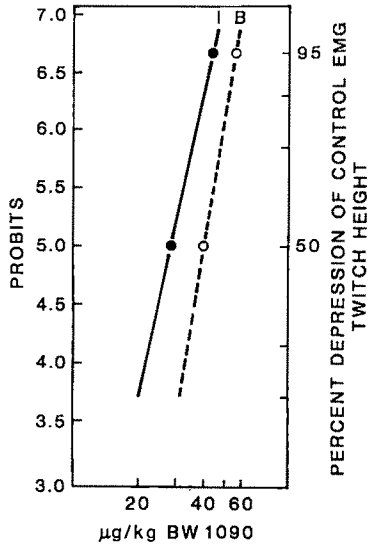

Figure 1. Mean dose–response curves for mivacurium (μg/kg) for adults during isoflurane anesthesia (I) or balanced anesthesia (B).

thesia (Fig. 1). This difference is statistically significant using a one-tailed t-test (i.e., assuming isoflurane would potentiate neuromuscular blockade).

The estimated ED_{95} for narcotic anesthesia (0.06 mg/kg) was given to nine patients during narcotic anesthesia and resulted in maximum neuromuscular blockade of 68 ± 37%, achieved in 5.9 ± 1.0 minutes (Table 3). A dose of 0.15 mg/kg mivacurium administered to seven patients during narcotic anesthesia resulted in a maximum block of 93 ± 18%, achieved in 3.8 ± 1.6 minutes. The estimated ED_{95} (0.05 mg/kg) for isoflurane anesthesia was given to nine patients during isoflurane anesthesia and resulted in a maximum neuromuscular blockade of 97 ± 5%, achieved in 4.5 ± 0.9 minutes. A dose of 0.1 mg/kg mivacurium in a group of nine patients resulted in a maximum block of 95 ± 11%, achieved in 4.4 ± 2.2 minutes during isoflurane anesthesia. The differences in both the maximum neuromuscular blockade and the times to maximum blockade are significantly different for the ED_{95} doses in the two groups, but not for the larger doses in the two groups.

Increasing the dose of mivacurium provides relatively little prolongation of action (Table 3). There was not a significant increase in duration when the dose of mivacurium was doubled from 0.05 to 0.10 mg/kg. The difference in average time to any endpoint of neuromuscular recovery between these two doses is about 2.0 minutes.

There was no significant change in MAP or HR as assessed by repeated measures analysis of variance during the first 5 minutes after bolus administration of mivacurium in those patients who received the largest dose of mivacurium during narcotic (0.15 mg/kg) or isoflurane (0.10 mg/kg) anesthesia. There were nine patients in each anesthetic group (Table 4). The greatest percentage decrease of MAP was 21%. This occurred 2 minutes after bolus administration of 0.15 mg/kg mivacurium. In this patient, as in the four other patients who experienced at least a 15% decrease in MAP, HR concurrently decreased 10% or less. Flushing of the face and torso after rapid intravenous administration of mivacurium was not observed in any patients. There were no adverse events

Table 3. Pharmacodynamics of Mivacurium in Adults

Anesthetic group and mivacurium dose	Time to maximum block (min)	Maximum block (%)	Time to recovery (min)				
			T5	T25	T50	T75	T95
BAL							
0.06 mg/kg	5.9 ± 1.0	68 ± 37	NA	10.5 ± 4.2	11.9 ± 4.1	14.1–4.4	16.0 ± 5.4
	(4.3–7.7)	(2–100)	12.2	(6.3–16.2)	(7.2–19.0)	(9–21.8)	(8.5–25.2)
	(9)*	(9)	(1)	(4)	(6)	(6)	(7)
0.15 mg/kg	3.8 ± 1.6	93 ± 18	11.3 ± 2.5	15.9 ± 4.2	18.8 ± 5.4	19.8 ± 7.4	26.0 ± 7.1
	(2.0–6.7)	(53–100)	(6.2–13.5)	(9.2–21.3)	(10.8–26.5)	(9–30.5)	(15.5–37.3)
	(7)	(7)	(7)	(6)	(6)	(7)	(6)
ISO							
0.05 mg/kg	4.5 ± 0.9	97 ± 5	10.1 ± 3.7	13.0 ± 5.0	16.8 ± 5.9	20.6 ± 7.9	25.7 ± 9.5
	(2.8–5.7)	(88–100)	(7–17.2)	(8.2–23.5)	(10.8–29.8)	(12.8–38.3)	(14.5–47.3)
	(8)	(8)	(6)	(8)	(8)	(8)	(8)
0.10 mg/kg	4.4 ± 2.2	95 ± 11	10.7 ± 4.0	15.0 ± 4.4	18.5 ± 4.6	21.5 ± 5.4	27.3 ± 7.2
	(1.8–8.7)	(67–100)	(4.8–16.2)	(9.2–23)	(11.5–26.5)	(14–29.8)	(19.2–39.3)
	(9)	(9)	(7)	(8)	(8)	(9)	(9)

*Values expressed as mean ± SD (range) (*n*).

Table 4. Effects of Mivacurium on Heart Rate and Blood Pressure

	Baseline	1 min	2 min	3 min	5 min
Group BAL (0.15 mg/kg)					
MAP (mm Hg)	73 ± 17	73 ± 14	70 ± 11	70 ± 11	71 ± 8
HR (beats/min)	78 ± 17	76 ± 17	75 ± 16	73 ± 16	71 ± 15
Group ISO (0.10 mg/kg)					
MAP (mm Hg)	74 ± 7	73 ± 8	74 ± 9	76 ± 16	73 ± 12
HR (beats/min)	77 ± 7	75 ± 6	76 ± 2	76 ± 2	74 ± 3

*Mean ± SD.

requiring clinical intervention after administration of mivacurium.

There was no significant difference between the recovery indexes described earlier (T25–T75) at different doses of mivacurium under the same anesthetic background. Therefore the dosage groups were combined. In the BAL group receiving either 0.06 or 0.15 mg/kg mivacurium, the recovery index was 5.5 ± 1.6 minutes (range 3.3–9.2 minutes, n = 10). In the ISO group, receiving either 0.05 or 0.10 mg/kg mivacurium, the recovery index was 7.4 ± 3.0 minutes (range 4–14.8 minutes, n = 16). The recovery index for the ISO group is significantly longer than that of the BAL group, using a one-tailed t-test (patients listed in Table 1 were not included in this analysis).

Discussion

This study was designed to compare the dose–response relations in adult surgical patients of mivacurium during nitrous oxide–narcotic (BAL) anesthesia and nitrous oxide–isoflurane (ISO) anesthesia. The addition of isoflurane to nitrous oxide significantly decreased the ED_{50} of mivacurium by about 25%, compared to the ED_{50} determined during nitrous oxide–narcotic anesthesia. Potent inhalation anesthetics are known to augment long-acting nondepolarizing relaxants in a dose (concentration)-related manner (9–11). The augmentation has been shown to be more marked with enflurane or isoflurane than with halothane. Intermediate-acting relaxants may not be augmented by potent anesthetics in the same manner (12,13). In our study, the end-tidal concentration of isoflurane was kept constant. Therefore, the relation between mivacurium bolus dose requirements during various depths of inhalation anesthesia remains to be determined.

The mean recovery index found for the BAL group was 5.5 minutes. The comparable recovery index in the ISO group was 7.4 minutes, indicating that isoflurane prolongs recovery from mivacurium-induced block, in addition to shifting the mivacurium dose–response relation leftward. It should be noted that the recovery indexes for mivacurium, under both balanced and isoflurane anesthesia, are still consid-

erably shorter than those reported for the intermediate- and long-acting nondepolarizing relaxants (14,15).

The clinical importance of the rapid recovery from mivacurium-induced block was demonstrated by a patient whose results were deleted from statistical analysis because of subclinical myositis diagnosed postoperatively. This patient received 0.05 mg/kg mivacurium and although recovery to 5% of initial baseline occurred in 17.7 minutes, 30 minutes more were required for his neuromuscular function to reach 50% of baseline. This recovery rate is threefold slower than that of any other patient (Table 3). If this patient had received a longer-acting neuromuscular blocking agent, postoperative ventilation would likely have been necessary. The patient's pseudocholinesterase activity and dibucaine number were within the normal range.

Some of the patients with low pseudocholinesterase activity (patients 3 and 4 in Table 1) demonstrated greater neuromuscular blockade than one would expect at a given dose and all but patient 1 required longer than was expected for initial recovery of neuromuscular function to appear. However, their recovery indexes were comparable to the recovery indexes for normal patients. This is difficult to explain. It is likely that the brief action of mivacurium is due to rapid enzymatic breakdown in plasma; however, the relative roles of the plasma enzymes and liver and kidney in terminating the action of mivacurium in vivo remain to be determined.

Previous work (16,17) has described a method for estimating the pharmacokinetic half-life of a drug from observations of effect. Briefly, doubling the dose of drug will produce a duration of action that is prolonged by the length of the elimination half-life of the drug. On this basis, our recovery data suggest that the plasma half-life of mivacurium is as short as several minutes.

Mivacurium has been reported to have cardiovascular side effects in some patients, most likely related to endogenous histamine release (3). It appears that the margin of safety for this side effect is roughly similar to atracurium and occurs in dose ranges 2.5 to 3 times the ED_{95}. In the doses evaluated in this study, however, no significant changes in heart rate or blood pressure occurred and no evidence of cutaneous flushing were noted after administration of mivacurium.

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Myocardial Oxygen Consumption and Segmental Shortening during Selective Coronary Hemodilution in Dogs

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CRYSTAL GJ, SALEM MR. Myocardial oxygen consumption and segmental shortening during selective coronary hemodilution in dogs. Anesth Analg 1988;67:500–8.

Experiments were conducted in 33 open chest, anesthetized dogs to evaluate direct effects of hemodilution on myocardial oxygenation and contractile function. The left anterior descending coronary artery (LAD) was perfused selectively from a controlled pressure reservoir with either normal arterial blood or arterial blood diluted with lactated Ringer's solution. Systemic hemodynamic parameters were held stable. In the LAD bed, values were obtained for coronary blood flow (CBF) with an electromagnetic flowmeter, myocardial oxygen consumption ($M\dot{V}O_2$) using the Fick principle, and percentage segmental shortening (%SS), an index of local myocardial contractility, by sonomicrometry. Studies were conducted with LAD perfusion pressure (PP) set at control (100 mm Hg) and at 50% of that level to simulate coronary insufficiency (CI). CI abolished coronary reactive hyperemia after release of a 90-second occlusion, indicating exhausted vasodilator reserve capacity. With PP at control, reductions in LAD hematocrit to as low as 10% had no effect on $M\dot{V}O_2$ or %SS, because increases in blood flow were sufficient to offset induced falls in arteriovenous oxygen content difference. However, during CI, a more modest reduction in hematocrit to 17% caused reductions in both $M\dot{V}O_2$ and %SS, because of inadequate flow responses during hemodilution. The following conclusions can be made: 1) Extreme hemodilution is well tolerated by the normal heart with a stable work requirement and; 2) Relatively modest hemodilution may compromise myocardial oxygenation and contractile function when in the presence of exhausted or severely depleted vasodilator reserve capacity.

Key Words: HEART, BLOOD FLOW—oxygen consumption. BLOOD—hemodilution.

Preoperative exchange of blood for cell-free solution is being used increasingly to decrease use of donor blood transfusions by use of autotransfusions (1). Maintenance of systemic oxygen transport in the face of the resultant condition of hemodilution is dependent on an increase in cardiac output to offset the reduction in arterial oxygen-carrying capacity (1). Therefore, the safe limit of hemodilution is closely related to how low the hematocrit can be reduced without jeopardizing myocardial oxygenation and the ability of the heart to sustain an augmented pumping requirement.

The numerous studies that have evaluated coronary and myocardial responses during hemodilution have yielded inconsistent findings (2–11). This is likely because of methodologic variations involving experimental design, animal model, and diluent, e.g., crystalloid vs colloid and also because of the variable influence of the systemic hemodynamic adjustments associated with whole-body exchange transfusions. These adjustments include increases in cardiac output, heart rate, myocardial contractility, and cardiac sympathetic drive (6,7,9–11), which are themselves important determinants of coronary blood flow and myocardial oxygen demands (12).

In the present study the direct effects of hemodilution on regional coronary hemodynamics, myocardial oxygen consumption, and myocardial segmental shortening were evaluated systematically under controlled conditions by perfusing a portion of the left anterior descending coronary artery in the in situ,

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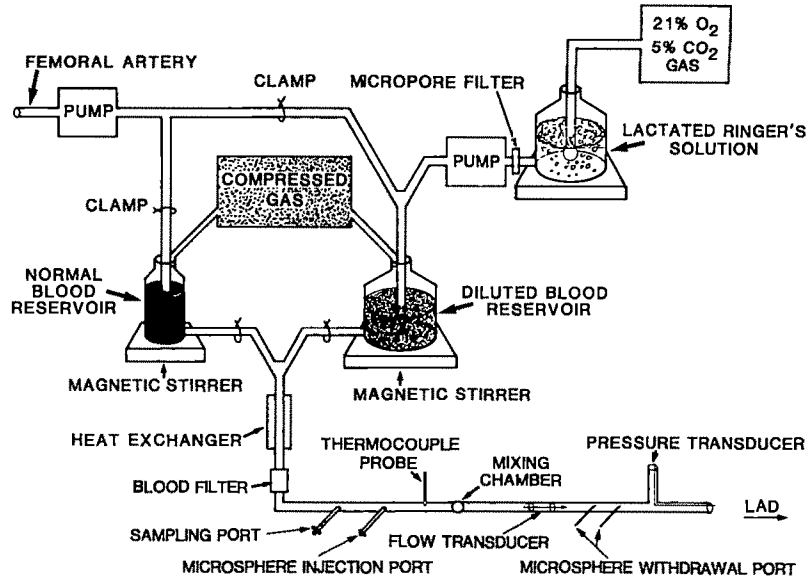

Figure 1. Extracorporeal system permitting selective perfusion of left anterior descending coronary artery with normal arterial blood or with arterial blood diluted with lactated Ringer's solution.

working canine heart with diluted but otherwise normal arterial blood. Because the remainder of the dog's body, including most of the heart, was perfused naturally via the aorta with arterial blood with normal hematocrit, the widespread hemodynamic changes that confounded interpretation of studies utilizing whole-body exchanges were avoided.

Our previous finding that autoregulatory coronary vasodilation along with reduced blood viscosity contributed to flow increases during local coronary hemodilution (13) infers reduced tolerance of myocardium to hemodilution in the presence of exhausted vasodilatory reserve capacity. To test this notion directly, studies were conducted with perfusion pressure normal and with it reduced by 50% to simulate a maximally dilating coronary stenosis.

Methods

Animal Preparation

Experiments were performed on 33 conditioned, heartworm-free mongrel dogs of either sex (weight range, 20–25 kg), anesthetized with pentobarbital sodium 30 mg/kg IV initially, with supplementation as required to maintain a stable anesthetic state. After tracheal intubation and left thoracotomy, the dog was ventilated by a Harvard respirator. Physiologic levels of arterial O_2 and CO_2 tensions (Table 2) were established by enriching the inspired air with oxygen and by adjusting the volume and rate of the respirator; these values were held constant during the experiment. Po_2, Pco_2, and pH of aortic as well as of coronary perfusate samples (see later) were measured electrometrically (Corning, model 111). The hematocrits of these blood samples were determined with a microcentrifuge. Body temperature was maintained at 38°C with a heating pad.

The pericardium was incised and the heart was suspended in a pericardial cradle. Polyethylene catheters were inserted into: 1) the thoracic aorta (via the right femoral artery) for measuring aortic pressure, 2) the right brachial artery for collecting samples of arterial blood, 3) the vena cava (via the right femoral vein) for intravenous injections and; 4) the left atrium (via the left atrial appendage) for measuring left atrial pressure. A micromanometer-tip pressure transducer (Millar Instruments) was inserted into the left ventricle via the left atrium and mitral valve to measure left ventricular pressure. The LAD was isolated approximately 2 cm from its origin for cannulation. After surgical procedures were completed, heparin 400 U/kg was administered to prevent blood coagulation.

A thin-wall stainless-steel cannula (2.5 mm inside diameter) was introduced into the isolated segment of the LAD, so that the artery could be perfused independently via an extracorporeal system with arterial blood with variable hematocrit (Fig. 1). The LAD perfusion line was equipped with an electromagnetic flow transducer to measure coronary blood flow using an electromagnetic flowmeter (Narco Bio-Systems). The flow transducer was calibrated in vitro with blood of variable hematocrits, so that signal output from the transducer could be converted into a flow rate under the wide range of hematocrits examined. LAD perfusion pressure was sensed through a small-diameter tube at the orifice of the perfusion cannula. The LAD perfusion line was equipped with

a heat exchanger to maintain temperature of blood perfusate at 38°C.

The perfusion system utilized two reservoirs, one for arterial blood with normal hematocrit (normal blood reservoir) and the other for arterial blood with reduced hematocrit (diluted blood reservoir). The reservoirs were connected to a large (20-L) air chamber that was pressurized to a desired perfusion pressure with compressed air. Because of the large air chamber, changes in blood volume of the aspirator bottles had minimal effect on LAD perfusion pressure. The reservoir bottles were positioned on a magnetic stirrer and their contents were continually stirred. Initially, both reservoirs were supplied with arterial blood with normal hematocrit obtained from the left femoral artery with a peristaltic pump. Arterial blood with normal gas composition but with variably reduced hematocrit was obtained in the diluted blood reservoir by the addition of lactated Ringer's solution, equilibrated with 21% O_2–5% CO_2 gas. Lactated Ringer's solution was selected as diluent because of its wide use clinically, and because, being a crystalloid, its tendency to distribute predominantly in the interstitial compartment minimized reductions in systemic hematocrit because of recirculation. When necessary, sodium bicarbonate was used to normalize the pH of low hematocrit blood. To minimize hemodepletion in experimental animals, blood from donor dogs was used to prime the perfusion system.

Aortic and left atrial blood pressures were measured with Statham transducers (model P23ID) and averaged electronically. The left ventricular pressure pulse was used to drive a cardiotachometer and it was differentiated to yield dP/dt max. LAD blood flow, blood pressures, myocardial segmental shortening (see later), and heart rate were recorded with a Gould recorder (model 2800S).

Determination of Myocardial Oxygen Consumption

When coronary anatomy permitted, a small-diameter (PE-90) catheter was implanted in the anterior interventricular coronary vein at same level as the LAD cannula. This catheter was allowed to drain freely to prevent venous stagnation and interstitial edema. Under steady-state conditions, samples of venous blood were collected anaerobically under mineral oil in a test tube, while samples of coronary perfusate were withdrawn directly from the LAD inflow circuit. Oxygen content of these blood samples was measured with a Lex-O_2-Con (Lexington Instruments) and was used to calculate the local arteriovenous oxygen content difference. This value was multiplied by LAD blood flow (measured electromagnetically) at the time the blood samples were obtained to calculate myocardial oxygen consumption using the Fick principle.

Measurement of Myocardial Segmental Length

Measurements of myocardial segmental length in the LAD bed were obtained by sonomicrometry (14). A pair of ultrasonic crystals were implanted into the LAD-perfused myocardium to a depth approximately midway between the epicardium and endocardium. Location in the LAD perfusion field and function of the crystals were verified by segmental lengthening during a brief (30-second) occlusion (Fig. 2). Changes in distance between the crystals were recorded from measurements of the ultrasonic transit time between the crystals (Triton Technology). The end-diastolic and end-systolic lengths (EDL, ESL) were identified by the beginning of the rapid increase in left ventricular pressure just before isovolumetric contraction and the peak negative dP/dt, respectively ([15], Fig. 2). Percentage segmental shortening (%SS) was calculated from the formula:

$$\%SS = [(EDL - ESL)/EDL] \times 100.$$

Statistical Analyses

Statistical analyses were performed using Student's *t*-test for paired samples (16). A value of $P<0.05$ was considered to reflect a statistically significant difference.

Experimental Protocols

Each exposure of LAD to diluted blood was preceded by a control period of perfusion with blood with normal hematocrit. Measurements in the LAD bed were obtained after attainment of steady-state conditions following change of perfusion conditions, which usually required approximately 3 minutes. Effects of hemodilution in LAD bed were evaluated with perfusion pressure maintained near mean aortic pressure and with it one-half of that value to stimulate coronary stenosis. This reduction in perfusion pressure was sufficient to abolish reactive hyperemia after release of a 90-second complete occlusion of LAD perfusion line. From one to three variations in LAD perfusion conditions were evaluated in each dog.

Under control conditions (normal hematocrit), arterial blood was pumped into the normal blood reservoir at a rate equal to the rate of blood supply to the LAD, which maintained isovolemic conditions in the experimental dog. During perfusion of LAD from the diluted blood reservoir, blood was withdrawn from the systemic circulation at a rate sufficient to maintain mean aortic pressure, an index of circulating blood volume, constant.

Results

Hemodilution with Normal Perfusion Pressure

Figure 2 presents sections of the original tracing showing characteristic hemodynamic responses under control conditions, coronary hemodilution, and total coronary occlusion. With perfusion pressure constant, hemodilution to a hematocrit of 22% caused a doubling of coronary blood flow. End-diastolic and end-systolic lengths both increased slightly during hemodilution; however, segmental shortening was not affected. Left ventricular dP/dt max, left ventricular pressure, aortic pressure, and heart rate remained at control levels during hemodilution. Left atrial pressure increased modestly. Systolic lengthening during complete occlusion of inflow line verifies that crystals were implanted in LAD-perfused myocardium.

Table 1 summarizes changes in myocardial oxygen consumption and segmental shortening during selective, graded hemodilution in LAD coronary artery with perfusion pressure maintained at control levels. Graded reductions in inflow hematocrit (range, 40–10%) caused proportional reductions in the arteriovenous oxygen content difference, but increases in coronary blood flow were sufficient to hold myocardial oxygen consumption at control levels. Percentage segmental shortening was also not affected by local hemodilution of any severity evaluated. Not shown in Table 1 is that LAD blood flow returned immediately to control levels upon reperfusion with blood with normal hematocrit, thus demonstrating reversibility of myocardial effects of hemodilution. Gas composition of LAD blood perfusate was maintained equal to that of aortic blood under control conditions (Table 2).

Table 2 summarizes changes in systemic hemodynamic variables during graded hemodilution. Under control conditions (normal LAD hematocrit), values for systemic hemodynamic variables were unremarkable. These variables remained essentially stable during coronary hemodilution.

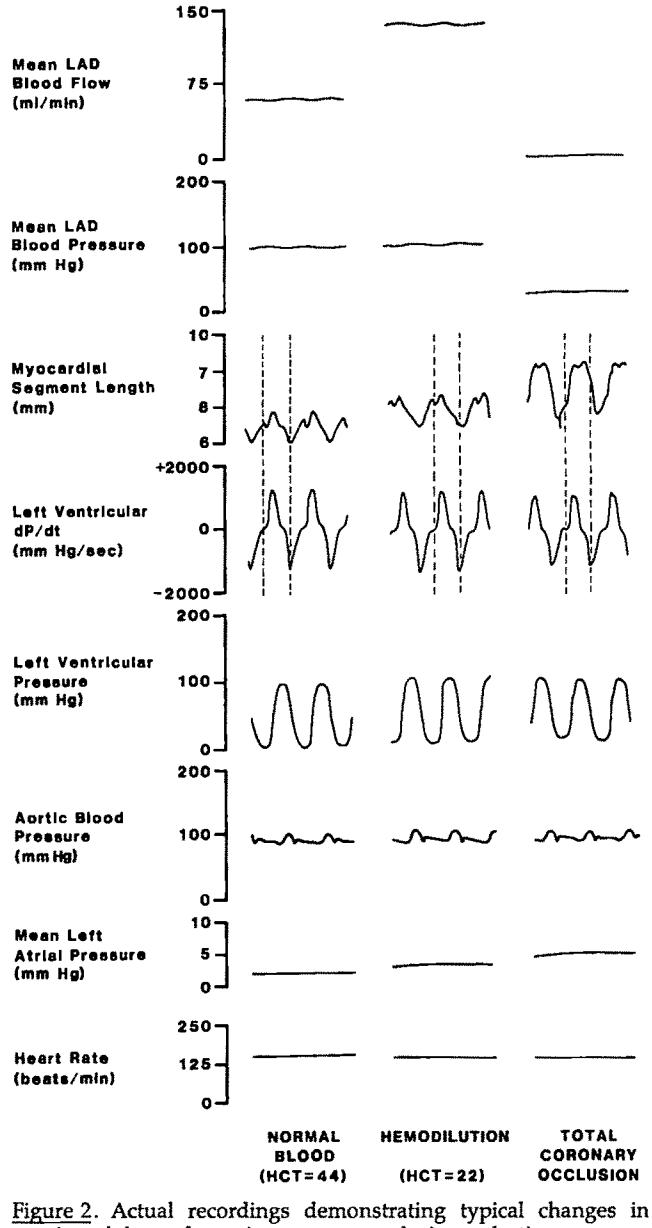

Figure 2. Actual recordings demonstrating typical changes in monitored hemodynamic parameters during selective coronary hemodilution and total coronary occlusion.

Hemodilution with Reduced Perfusion Pressure

Table 3 summarizes effects of reduced LAD perfusion pressure alone and in combination with local hemodilution. With LAD hematocrit normal, a reduction in perfusion pressure of 50% caused a 29% decrease in blood flow which, in the presence of a 34% increase in the arteriovenous oxygen difference, resulted in a 19% decrease in myocardial oxygen consumption. Percentage segmental shortening was unaffected.

In contrast, with LAD hematocrit reduced, a 50% reduction in perfusion pressure caused an essentially proportional reduction in coronary blood flow. Because this reduction in flow was accompanied by no change in coronary arteriovenous oxygen difference,

Table 1. Local Myocardial Oxygen Consumption and Segmental Shortening during Selective, Graded Hemodilution in Left Anterior Descending Coronary Artery

		Reductions in coronary hematocrit (%)		
	Control	25–35	15–25	<15
MVo (ml/min)*	2.67 ± 0.20†	2.46 ± 0.24	2.36 ± 0.21	2.74 ± 0.44
	(27)	(7)	(11)	(9)
CBF (ml/min)	44 ± 3	69 ± 14‡	100 ± 14‡	135 ± 11‡
	(35)	(12)	(12)	(11)
A-V 0_2 (vol%)	6.2 ± 0.4	5.2 ± 0.3‡	2.9 ± 0.4‡	2.1 ± 0.3‡
	(27)	(7)	(11)	(9)
%SS	12.9 ± 0.9	12.7 ± 1.1	11.9 ± 1.2	12.0 ± 1.6
	(35)	(12)	(12)	(11)
End-diastolic length (mm)	10.4 ± 0.5	10.5 ± 1.2	11.0 ± 0.8	10.7 ± 1.1
	(35)	(12)	(12)	(11)
End-systolic length (mm)	9.2 ± 0.5	9.5 ± 0.8	9.6 ± 0.7	9.6 ± 1.1
	(35)	(12)	(12)	(11)
Arterial Hct (%)	39 ± 1	28 ± 1‡	20 ± 1‡	11 ± 1‡
	(35)	(12)	(12)	(11)
Venous HCT (%)	40 ± 1	29 ± 2‡	21 ± 1‡	12 ± 1‡
	(28)	(8)	(11)	(9)
CPP (mm Hg)	98 ± 1	100 ± 3	98 ± 3	96 ± 2
	(35)	(12)	(12)	(11)

*Abbreviations: $M\dot{V}o_2$myocardial oxygen consumption; CBF, coronary blood flow; A-V O_2, arteriovenous oxygen content difference; %SS, percentage segmental shortening; arterial Hct, coronary artery hematocrit; venous Hct, coronary venous hematocrit; CPP, coronary perfusion pressure.
†Values are mean ± SE Numbers in parentheses are observations.
‡$P < 0.05$ from respective control.

Table 2. Stability of Systemic Hemodynamic Parameters during Selective, Graded Hemodilution in Left Anterior Descending Coronary Artery

		Reductions in coronary hematocrit (%)		
	Control	25–35	15–25	<15
Aortic pressure (mm Hg)	90 ± 2*	88 ± 5	94 ± 4	94 ± 4
Left atrial pressure (mm Hg)	5.0 ± 0.4	6.1 ± 0.6†	5.5 ± 0.8†	7.8 ± 0.9†
LV dP/dt max (mm Hg/sec)	1308 ± 33	1365 ± 62	1231 ± 91	1405 ± 53
Heart rate (beats/min)	140 ± 3	139 ± 7	143 ± 6	144 ± 4
Aortic blood values				
Po_2 (mm Hg)	149 ± 14	139 ± 26	177 ± 24	121 ± 18
Pco_2 (mm Hg)	42 ± 1	41 ± 1	44 ± 3	44 ± 2
pH	7.34 ± 0.01	7.35 ± 0.01	7.33 ± 0.02	7.35 ± 0.02
Hematocrit (%)	39 ± 1	41 ± 2	37 ± 2	32 ± 3†
Observations	35	12	12	11

*Values are mean ±SE.
†$P < 0.05$ from respective control.

it resulted in a parallel reduction in myocardial oxygen consumption. Combining hypotension with hemodilution caused a 42% decrease in percentage segmental shortening.

Neither hypotension alone nor hypotension combined with hemodilution affected systemic hemodynamic variables. Values remained similar to those presented for the control condition in Table 2.

Discussion

Critique of Methods

Previous studies of effects of hemodilution on coronary hemodynamics and myocardial oxygenation utilized whole-body exchange transfusions which, because they were accompanied by changes in systemic hemodynamic parameters and global cardiac function (6,7,9–11), yielded ambigous results. This problem was circumvented in the present study by use of an extracorporeal perfusion system to confine hemodilution to a circumscribed region of the left ventricular free wall.

The canine heart preparation employed in the present study to perfuse selectively the left anterior descending coronary bed with diluted blood has been used previously to evaluate direct coronary effects of other physiologic conditions (e.g., hypoxemia [17]) and drugs, including adenosine (18). This prepara-

Table 3. Local Myocardial Effects of Coronary Hypotension during Perfusion of LAD with Arterial Blood with Normal Hematocrit or with Low Hematocrit

	Normal hematocrit		Low hematocrit	
	Control	Hypotension	Control	Hypotension
$M\dot{V}o_2$ (ml/min)*	3.00 ± 0.38† (7)	2.43 ± 0.14‡ (7)	3.92 ± 0.59 (5)	1.75 ± 0.27‡ (5)
CBF (ml/min)	35 ± 7 (22)	25 ± 4‡ (22)	147 ± 20 (11)	57 ± 7‡ (11)
A-V 0_2 (vol%)	7.9 ± 0.6 (7)	10.6 ± 0.9‡ (7)	3.2 ± 0.7 (5)	4.1 ± 1.2 (5)
%SS	15.6 ± 1.3 (22)	14.9 ± 1.2 (22)	16.0 ± 2.6 (11)	9.3 ± 2.3‡ (11)
End-diastolic length (mm)	10.3 ± 0.5 (22)	10.1 ± 0.5 (22)	10.5 ± 0.8 (11)	10.6 ± 0.8 (11)
End-systolic length (mm)	8.3 ± 0.5 (22)	8.6 ± 0.5 (22)	8.9 ± 0.8 (11)	9.7 ± 0.9‡ (11)
Arterial Hct (%)	44 ± 2 (22)	44 ± 2 (22)	18 ± 2 (11)	17 ± 2 (11)
CPP (mm Hg)	101 ± 1 (22)	50 ± 1‡ (22)	96 ± 3 (11)	50 ± 1‡ (11)

*Abbreviations as in Table 1.
†Values are mean ± SE. Numbers in parentheses are observations.
‡$P < 0.05$ from respective control.

tion results in basal values for hemodynamic metabolic, and functional parameters in the perfused bed similar to those in the naturally supplied bed. Furthermore, normal responsivity to vasodilator stimuli is preserved.

The finding that hematocrit of venous blood samples collected from the anterior interventricular coronary vein changed in parallel with induced changes in LAD hematocrit (Table 1) indicates that this vein provided samples of venous effluent from LAD-dependent myocardium. This finding confirms earlier studies that mapped left coronary venous drainage patterns using inert gas tracers (19) or chromium-labeled red blood cells (20).

The location and orientation of the crystal pair were important considerations in utilizing the sonomicrometric technique to evaluate the influence of local coronary hemodilution on myocardial segmental shortening. Location within the LAD perfusion field was verified by demonstrating systolic bulging during a brief 30-second occlusion of the perfusion tubing. Furthermore, the crystals were oriented so that they were parallel with the anticipated direction of myocardial fibers in the left ventricular midwall (21).

Collateral flow results when a pressure gradient is produced between two adjacent coronary arteries. Such would be the case in the present study when inflow pressure was reduced by one-half selectively in the left anterior descending coronary artery. Collateral flow was not measured in the present study, but previous measurements obtained with radioactive microspheres under identical conditions indicated that it contributes only 3% of total perfusion of LAD-dependent myocardium (22). Thus, unmeasured collateral flow would not introduce sufficient errors into the estimates of myocardial oxygen consumption to invalidate any of our conclusions.

Myocardial Effects of Local Hemodilution

Although oxygen extraction in the coronary vascular bed is generally higher than that in other beds, an extraction reserve exists that can be tapped when necessary to maintain myocardial oxygenation. This mechanism was evident in the present study during selective coronary hypotension (Table 3). The finding that coronary arteriovenous oxygen differences decreased in parallel with inflow hematocrit infers that this extraction reserve was not utilized during hemodilution. This is in keeping with previous reports of constant or even elevated coronary venous oxygen tension during hemodilution (13). Several mechanisms have been proposed to account for this apparent impediment to myocardial oxygen extraction (11). They include: 1) a flow-limited diffusion of oxygen, 2) an arteriovenous shunt diffusion of oxygen, 3) alterations in the oxygen-binding properties of blood due to altered plasma protein and buffer content and, 4) reduced oxygen release from red cells due to diminished intracellular convection. A systematic evaluation of these mechanisms is beyond the scope this study.

Because of the limitation on oxygen extraction during hemodilution, myocardial oxygenation can be maintained only if increases in coronary blood flow are sufficient to compensate for reduced arterial oxygen content. Under conditions of constant perfusion pressure, this was the case, because myocardial oxygen consumption and contractile function remained normal despite significant reductions in coronary hematocrit to as low as 10%. Our previous finding of transmurally uniform left ventricular blood flow during local hemodilution (13) implies that oxygen supply was equally well maintained across the left ventricular free wall, assuming absence of significant diffusional loss of oxygen from transmurally penetrating coronary conducting vessels.

With perfusion pressure constant, increases in coronary blood flow during hemodilution reflected decreases in local vascular resistance. One factor reducing vascular resistance during hemodilution was decreased blood viscosity (23). However, the fact that increases in flow were just adequate to maintain local myocardial oxygen demands suggests that another factor, metabolically coupled, autoregulatory increases in vessel caliber (14), fine-tuned the reductions in coronary vascular resistance. A role for such a mechanism is consistent with our previous observation of reduced coronary vasodilator reserve capacity during local hemodilution (13). The metabolite responsible for coronary vasodilation is a matter for speculation. Although adenosine, a breakdown product of ATP, has been implicated in local regulation of coronary blood flow under a variety of conditions, including increased metabolic demand, hypoxemia, and reactive hyperemia (14), its contribution to vasomotor adjustments during hemodilution awaits elucidation.

In contrast to the present findings, previous studies utilizing whole-body exchange transfusions demonstrated that myocardial oxygen consumption could be maintained only if hematocrit remained above 20% (7). This apparent conflict may be explained by the decreases in diastolic aortic pressure (coronary driving pressure) and the associated tachycardia observed when severe hemodilution is induced systemically. Each of these factors restricts blood flow in dilated coronary circulations, particularly in the subendocardium (12).

The dependence on autoregulatory vasodilation during coronary hemodilution inferred increased vulnerability of myocardium to this condition in the presence of compromised vasodilator reserve capacity (13). This notion was tested directly in the present study by evaluating the influence of reduced perfusion pressure on changes in myocardial oxygen consumption and segmental shortening during local hemodilution. The 50 mm Hg reduction in perfusion pressure selected for study was sufficient to maximally dilate the coronary vasculature, as demonstrated by lack of reactive hyperemia after release of a 90-second occusion (24), and was the equivalent of a 90% stenosis of the LAD (25).

To provide a reference for assessing myocardial effects of coronary hypotension during hemodilution, we first identified effects of hypotension with hematocrit normal. Under this condition, reductions in coronary blood flow were less than proportional to induced reductions in perfusion pressure, which inferred vasodilation. Such vasodilation is an example of the intrinsic tendency of the coronary circulation to maintain relatively constant flow in the face of variations in driving pressure, so-called pressure-flow autoregulation (12). This factor, along with augmented oxygen extraction, contributed to the maintenance of myocardial oxygen consumption and contractile function during low-pressure perfusion of normal arterial blood. Others (25–27) have reported no change in local myocardial function during similar degrees of regional coronary hypotension in canine hearts.

Because the midwall positioning of the crystal pair that we used was relatively insensitive to changes in subendocardial segmental shortening, it cannot be assumed that selective subendocardial dysfunction did not occur during coronary hypotension. Indeed, the greater decrease in subendocardial blood flow compared with subepicardial blood flow demonstrated previously (13) and the modest reduction in regional myocardial oxygen consumption found in the present study suggest this possibility.

In contrast to findings during perfusion with normal blood, reducing perfusion pressure during hemodilution caused significant impairment to myocardial oxygenation, and contractile function deteriorated. This difference in response appears dependent on the lack of augmented oxygen extraction and of autoregulatory vasodilation when hypotension was induced during hemodilution. The limitation to oxygen extraction during hemodilution was discussed earlier in reference to findings at normal perfusion pressure. The fact that oxygen extraction did not increase when the rate of coronary flow was reduced by hypotension argues that the limitation to extraction under conditions of normal perfusion pressure was not attributable to flow-limited diffusion for oxygen (see earlier). The absence of autoregulatory vasodilation is demonstrated by decreases in coronary blood flow that were parallel to induced reductions in perfusion pressure. This likely reflects deple-

tion of the vascular reserve by vasodilation during hemodilution alone.

Because coronary resistance vessels were maximally dilated by endogenous factors during hypotension (no reactive hyperemia), the ability of hemodilution to increase blood flow under that condition reflects the effect of reduced blood viscosity itself. Although these flow increases were quite marked, they were not adequate to maintain myocardial oxygenation and segmental shortening at levels during hypotension alone. These findings reaffirm the requirement for a recruitable vasodilator reserve capacity for maintenance of myocardial oxygen supply/demand balance during hemodilution. The present findings clarify previous studies demonstrating regional myocardial dysfunction when a flow-limiting coronary stenosis was induced during systemic hemodilution (28), although the data were complicated by increases in cardiac output which, at constant arterial pressure, increased myocardial oxygen demands (29) and thus may have aggravated ischemia.

Previous measurements of regional myocardial blood flow indicated that the relative underperfusion of subendocardium during coronary hypotension with normal arterial blood perfusate persisted when perfusate was switched to blood diluted with lactated Ringer's solution (13), which suggests that oxygen deficit and functional impairment may be magnified in this region.

Clinical Applications

The present results provide new fundamental information on the intrinsic ability of the coronary circulation to maintain myocardial oxygenation during hemodilution. They should be extrapolated to humans only with caution for three reasons. First, selective coronary hemodilution is an unnatural condition that does not occur clinically. Second, barbiturate anesthesia and thoracotomy alter cardiac responsivity (30). Third, the experimental model of acute low-pressure coronary perfusion ignores the influence of the well-developed collateral circulation, which often accompanies long-standing coronary artery disease (31). Nevertheless, the present findings provide broad guidelines for assessing when hemodilution can be utilized without jeopardizing cardiac function. They suggest that hemodilution of a relatively extreme extent may be used safely when systemic hemodynamic parameters are normal and coronary arteries are not obstructed. Although we observed no change in regional oxygen consumption and segmental shortening with hematocrits as low as 10%, this value would no doubt vary from patient to patient, depending on a variety of factors including drug status, age, blood substitute, (e.g., colloid or crystalloid), body temperature, etc. Our results also suggest that even moderate hemodilution may be unsafe in patients in whom coronary vasodilatory reserve is exhausted or severely depleted by proximal stenosis, hypoxemia, or increased myocardial metabolic demand secondary to hypertension, valvular heart disease, fever, or anesthesia.

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Effects of Intrathecal Fentanyl and Lidocaine on Somatosensory-Evoked Potentials, the H-Reflex, and Clinical Responses

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CHABAL C, JACOBSON L, LITTLE J. Effects of intrathecal fentanyl and lidocaine on somatosensory-evoked potentials, the H-reflex and clinical responses. Anesth Analg 1988;67:509–13.

Intravenous narcotics increase the latency of somatosensory-evoked potentials (SSEPS), which are decreased but not abolished by epidural local anesthetics. In addition, intrathecal narcotics decrease spasticity in patients with central nervous system disease. This study of the effects of intrathecal fentanyl on posterior tibial SSEPS and the monosynaptic H-reflex arc found that intrathecal fentanyl had no effect on the latency of SSEPS, indicating the effects of narcotics on SSEPS are likely to exist at a supraspinal level. H-reflexes were not affected, confirming the lack of effect on this spinal motor reflex. In the same group of patients, intrathecal lidocaine administered 1 week later completely abolished SSEPS and H-reflexes. Complete suppression of SSEPS corresponded to full motor blockade, but sensation to pain and temperature was already many dermatomes higher than the S_1 level. Return of SSEPS occurred with return of motor but not sensory function, indicating the likelihood that SSEPS are carried at least in part by large A-fibers. The study shows that spinal narcotics neither affect the transmission of SSEPS nor decrease the H-reflex, a spinal motor reflex. In addition, changes in SSEPS after intrathecal lidocaine do not correlate with the level of surgical anesthesia.

Key Words: ANALGESICS—fentanyl.
ANESTHETIC TECHNIQUES, SPINAL—fentanyl.
BRAIN—evoked responses.

Somatosensory-evoked potentials (SSEPS) have been used to aid in the diagnosis and evaluation of central nervous system pathology (1,2), to provide a monitor of central nervous system integrity during operations (3), and to aid in basic research on the organization and physiology of the nervous system (4,5). Utilization of SSEPS during operative procedures has concentrated on outcome data. Case reports have predicted and/or warned of impending neurologic damage when nerve pathways have been compressed or vascular integrity compromised (6–8).

The effects of anesthetics and analgesics on SSEPS indicate that SSEPS may be a valuable tool in understanding neurophysiologic pathways, mechanisms, and the effects of these drugs on sensory transmission (4,5). This study examined and compared the effects of intrathecal lidocaine and fentanyl on posterior tibial SSEPS and correlated the clinical findings with the SSEPS findings. In addition, it is believed that neuralaxial narcotics have little effect on motor tone in neurologically intact humans; thus, the H-reflex, a monosynaptic spinal motor loop, was monitored and the effects of both drugs on this reflex were studied (9).

Methods

After obtaining Human Subjects Committee approval and FDA permission to use fentanyl by the intrathecal route, eight subjects with chronic pain were investigated on consecutive weeks using diagnostic opioid and local anesthetic spinal anesthetic spinal blocks. On week 1, the subjects received an intrathecal injection of 25 μg fentanyl mixed with 0.5 ml spinal fluid for a total of 1 ml. One week later subjects received 50 mg lidocaine in 5% dextrose (1 ml). Injections were at the L2–3 level. Baseline SSEPS were measured before the procedure. The posterior

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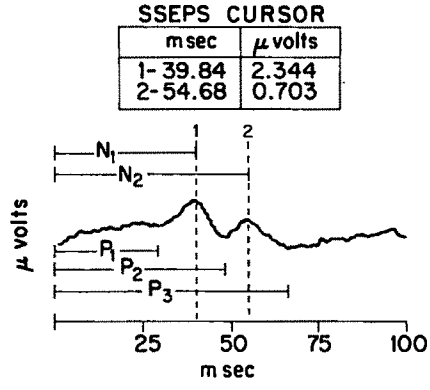

Figure 1. Typical baseline posterior tibial SSEPS with illustration of component nomenclature.

tibial nerve was stimulated with surface electrodes placed posterior to the medial malleolus at the ankle. Stimulation intensity was just above muscle twitch threshold and at a level at which subjects reported some discomfort. Recording electrodes were placed on the scalp at Fz and Cz prime (International Ten Twenty System). Recordings were made with a Neurotrac signal averager using 256 repetitions, at 5 stimuli per second, and a recording interval of 100 milliseconds. After stable baseline recordings were obtained, the diagnostic block was performed and SSEPS recorded at 5, 15, 30, and 60 minutes, then at 30-minute intervals until the SSEPS returned to baseline or for a minimum of 2 hours after the injection of fentanyl or lidocaine. In addition, measurements of sensation to pinprick, temperature, and muscle strength, using a modified Bromage Scale (10) (0, ability to raise extended leg against gravity; 1, inability to raise extended leg; 2, inability to flex the knee; 3, inability to dorsiflex the ankle) were made at 5 and 10 minutes after drug injection and then at the same intervals as SSEPS were recorded. SSEPS were labeled and analyzed with methods similar to those reported by Saugbjerg et al. (11). The first downward deflection is labeled P1, the first upward deflection N1, the second downward deflection P2, etc. An example of a typical posterial tibial SSEPS is shown in Figure 1. Baseline amplitude measurements were variable between serial recordings and were not included in data analysis.

H-reflexes were also measured on the contralateral leg at the same time SSEPS measurements were made using a Cadwell Quantum 84 four-channel EMG. Stimulus was at the popliteal fossa with recordings made over the soleus muscle. The data were analyzed to evaluate changes in latency and paired Student's *t*-tests, comparing baseline values with values obtained at various times postinjection, were used to determine statistical significance of observed changes. Statistical significance was accepted with levels of $P < 0.05$. In addition, clinical findings were correlated with electrophysiologic measurements.

Results

Latency values of SSEPS after intrathecal fentanyl are shown in Table 1. H-reflex, amplitude, and latency values after intrathecal fentanyl are shown in Tables 2 and 3. There were no significant changes associated with intrathecal fentanyl in either posterior tibial SSEPS or H-reflexes.

Intrathecal lidocaine completely abolished both SSEPS and H-reflexes. The time at which SSEPS were abolished, time of return to baseline SSEPS, and corresponding clinical findings are shown in Table 4. Loss of SSEPS was accompanied by onset of motor and sensory neural blockade. Loss of pinprick and temperature sensation preceded loss of SSEPS in all cases. Significant neural blockade, including complete motor block, was necessary to abolish SSEPS. At return of SSEPS activity, most patients still had significant sensory blockade, several dermatomes above the L5–S_1 level; however, motor strength was nearly at control levels.

Discussion

SSEPS have been used as an intraoperative monitoring aid for many years. Halogenated anesthetics (12–15) and nitrous oxide (16), for example, affect SSEPS. Both intravenous bolus injections and continuous infusions of fentanyl or morphine also modify SSEPS recorded after stimulation of either the posterior tibial nerve or tooth pulp (17,18). In the study by Pathak et al. (17), there were consistent increases in latencies after both intravenous fentanyl and morphine with less, consistent changes in amplitude. The present study was undertaken to determine if changes in SSEPS were modulated at the dorsal horn level. With intrathecal administration of the lipid soluble fentanyl, concentrations of fentanyl in the dorsal horn would greatly exceed levels obtained by intravenous infusion. In addition the narcotic effects would be largely limited to the spinal level. The results of a recent study using epidural morphine (4) and the present study with intrathecal fentanyl indicate that the transmission of SSEPS are not affected by high levels of narcotics at the dorsal horn and thus the previously described changes associated with intravenous narcotics (17) are likely from a supraspinal action.

Table 1. Latency Values (milliseconds) of Somatosensory-Evoked Potential Components after Intrathecal Fentanyl (25 μg)*

	Time after intrathecal injection (minutes)									
Patients	Before	15	30	60	90	Before	15	30	60	90
	N1					N2				
1	43.7	1.00	1.01	1.02	1.00	66.4	0.99	0.99	1.00	1.00
2	52.0	1.00	1.00	1.00	1.00	80.4	1.00	1.00	0.99	0.99
3	62.0	1.00	1.02	1.02	1.02	82.8	1.00	1.00	1.01	0.98
4	42.1	0.98	1.02	0.99	1.02	64.8	0.97	1.01	1.01	1.01
5	37.9	1.00	1.00	0.97	1.00	57.5	1.00	0.99	0.99	0.98
6	37.5	1.00	1.00	1.02	1.02	51.0	1.01	1.02	1.03	1.03
7	41.0	1.02	1.00	1.01	1.01	62.0	0.98	0.98	1.01	1.01
8	38.0	0.99	0.97	0.95	1.02	52.9	0.98	0.97	0.97	0.98
Mean		0.99	1.00	0.99	1.01	Mean	0.99	0.99	1.00	0.99
±SD		± 0.04	± 0.02	± 0.04	± 0.11	±SD	± 0.04	± 0.04	± 0.03	± 0.02
	P2					P3				
1	50.0	1.00	1.10	1.02	0.99	85.1	1.00	1.01	1.01	0.99
2	58.6	1.00	1.00	1.02	1.00	94.0	1.01	1.01	0.98	1.00
3	70.3	1.00	1.02	0.99	1.01	96.0	1.00	1.00	0.98	0.99
4	52.3	1.01	1.00	1.01	0.99	75.1	1.01	1.01	1.01	1.01
5	47.5	1.03	1.01	1.01	1.01	72.7	0.97	0.99	1.00	1.00
6	46.0	1.00	1.00	1.02	1.02	76.0	1.00	1.00	1.01	1.01
7	48.0	1.01	1.01	1.02	1.02	76.0	1.00	1.03	1.01	1.01
8	45.8	0.96	0.96	0.96	1.01	60.0	1.02	1.00	1.03	1.05
Mean		1.01	1.01	1.02	1.00	Mean	1.00	1.02	1.00	1.00
±SD		± 0.03	± 0.04	± 0.11	± 0.01	±SD	± 0.03	± 0.16	± 0.03	± 0.01

*Values after injection are expressed as ratio of observed/baseline (before). P1 not present in many patients. (Changes between baseline values and values for each time frame not statistically significant, $P > 0.1$).

Table 2. H Amplitude and Peak–Peak (mV) after Intrathecal Fentanyl*

	Time after intrathecal injection (minutes)				
Patients	Before	15	30	60	90
1	8.10†	0.96	0.90	0.90	0.90
2	1.20	1.40	0.84	1.16	1.25
3	0.69	1.00	1.13	1.50	1.73
4	5.60	0.98	1.16	1.00	1.00
5	4.90	1.08	1.02	1.14	1.14
Mean		1.08	1.01	1.14	1.2
±SD		± 0.14	± 0.12	± 0.23	± 0.32

*Values expressed as ratio of observed/baseline (before).
†($P > 0.1$).

Table 3. H-Latency to First Deflection (milliseconds) at Times after Intrathecal Injection*

	Time after intrathecal injection (minutes)				
Patients	Before	15	30	60	90
1	29.58†	1.00	1.00	1.00	1.00
2	36.25	1.01	1.02	1.09	1.01
3	34.58	1.00	1.06	1.04	1.04
4	37.50	0.98	0.98	1.01	1.01
5	30.83	0.98	0.96	0.97	0.97
Mean		1.99	1.00	1.02	1.00
±SD		± 0.01	± 0.04	± 0.05	± 0.02

*Values expressed as ratio of observed/baseline (before).
†($P > 0.1$).

Because spinal cord modulation of pain is via C or A-δ fibers and conventional monitoring techniques usually record 50 to 100 milliseconds after the stimulus, it is possible that delayed changes in SSEPS may be missed. Although this may be true for C-fibers, changes in A-δ fiber activity should still be detectable using conventional techniques. This is supported by work in cats and humans demonstrating small fiber A-δ contribution to early components of SSEPS (<60 milliseconds) (19,20). In addition, Pathak et al. (17), using both stimulation intensity and recording intervals similar to those used in the present study, demonstrated consistent increases in SSEPS latency after intravenous narcotics.

The present group of patients given intrathecal fentanyl were 1 week later given intrathecal lidocaine that completely abolished SSEPS. Interestingly, the sensory changes to pinprick and temperature (small fibers) preceded changes in SSEPS and motor function. Conversely, when the local block receded,

Table 4. SSEPS and Clinical Findings* after Intrathecal Lidocaine

Patients	Time to abolished SSEP (minutes)	Clinical assessment			Time to baseline SSEP (minutes)	Clinical assessment		
		Pin	Temp	Motor		Pin	Temp	Motor
1	15	T11	T9	3	150	L3	T10	1
2	5	T7	T4	3	90	L1	T10	0
3	15	T12	T10	3	150	L4	T12	0
4	30	T4	T4	3	180	L5	L1	0
5	15	T10	T4	3	90	T6	T6	1
6	30	T10	T8	3	180	L4	L1	0
7	15	T10	T7	3	90	T12	T10	1

*Clinical assessment noted the dermatomal level at which a patient could feel a pin and discriminate temperature changes. Motor function was assessed using the modified Bromage scale 0–3.

SSEPS often returned to baseline with corresponding return of at least partial motor function, but often a sensory blockade persisted that was several dermatomes cephalad to the S_1 nerve root. This observation is supported by other studies that have noted little correlation between SSEPS and dermatomal sensation after epidural bupivacaine (11,21). In these other studies, epidural injection of 0.5% bupivacaine produced an increase in the latency and decrease in the amplitude of the SSEPS, but at no point were the SSEPS abolished. Clinical examination after the epidural injection of bupivacaine showed sensory blockade to the midthorax region but an incomplete motor blockade (11,21). In the present study intrathecal lidocaine completely abolished SSEPS only after total motor blockade, and return of SSEPS as the anesthesia wore off corresponded to at least partial return of motor function, thus indicating the likelihood that SSEPS are carried at least in part by large myelinated A-fibers. If true, early changes in SSEPS associated with A-δ or C-fiber conduction may be masked by the persistent SSEPS carried by the larger A-fibers. It appears that conventionally recorded posterior tibial SSEPS provide a correlation that most closely approximates blockade of somatic motor nerves, not the level of surgical analgesia. In addition, the data support the clinical impression that although epidural agents may provide adequate surgical analgesia, a more complete anesthesia may be obtained with subarachnoid injection. Perhaps peripheral stimulation with means more specific to A-δ or C-fibers (22) may yield a better correlation with SSEPS and the level of surgical analgesia.

Narcotics, particularly intrathecally administered, have recently been shown to decrease spasticity (23). This effect could possibly be due to a modulation via interneurons on reflex pathways. In animals, morphine is an effective activator of Renshaw cells and spinal interneurons (24,25), and in humans neuraxial narcotics depress a polysynaptic pain withdrawal reflex (26). The present study shows a lack of effect of intrathecal fentanyl on either latency or amplitude of the monosynaptic H-reflex. This supports the impression that intrathecal narcotics have little effect on spinal reflex arcs in normal subjects (9). The effect on patients with upper motor neuron pathology remains to be demonstrated.

In summary, although intravenous narcotics increase the latency of SSEPS, it appears that this effect is not due to modulation of SSEPS at the dorsal horn level. In addition the lack of effect of intraspinal narcotics on a spinal motor reflex in animals has been confirmed in neurologically intact humans. SSEPS changes demonstrated with intrathecal lidocaine correlated with somatic motor blockade but not with levels of sensory anesthesia or temperature discrimination. Posterior tibial SSEPS are useful for intraoperative monitoring of the integrity of neural pathways and motor blockade during spinal anesthesia, but not the level of surgical anesthesia.

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Mechanisms of Enhanced Canine Subendocardial Perfusion

A Comparison of Adenosine Triphosphate and Sodium Nitroprusside

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PELC LR, GROSS GJ, KAMPINE JP, WARLTIER DC. Mechanisms of enhanced canine subendocardial perfusion: a comparison of adenosine triphosphate and sodium nitroprusside. Anesth Analg 1988; 67:514–20.

The purpose of these experiments was to determine the effects of adenosine triphosphate (ATP) and sodium nitroprusside, two compounds used to produce controlled hypotension during surgery, on regional myocardial blood flow. Intracoronary drug infusions in open chest, anesthetized dogs were used to study the direct actions of these agents on the coronary circulation as well as to avoid systemic hemodynamic effects. The actions of the endothelium-dependent and -independent vasodilators, ATP and nitroprusside, respectively, were studied before and after administration of quinacrine (an inhibitor of phospholipase A_2), which blocks formation and/or release of endothelium-derived relaxing factor (EDRF). Both vasodilators produced significant increases in transmural blood flow of the drug-perfused zone. Only ATP, the endothelium-dependent vasodilator, altered the distribution of myocardial blood flow. Perfusion to the subendocardium was preferentially increased by ATP, resulting in an increase in the subendocardial-to-subepicardial flow ratio. Quinacrine markedly inhibited the increase in endo/epi produced by ATP without changing total flow. These data suggest that ATP increases total coronary blood flow by a mechanism that is independent of EDRF, but the selective redistribution of blood flow to the subendocardium is dependent on EDRF. Nitroprusside, an endothelium-independent vasodilator, produces no redistribution of myocardial blood flow.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—ATP. HEART, CORONARY BLOOD FLOW —Oxygenation.

Controlled hypotension during anesthesia is used to decrease blood loss and produce a more optimum surgical field. Sodium nitroprusside is commonly utilized but recently adenosine triphosphate (ATP) has also been proposed as an agent potentially useful for this purpose (1). Whereas considerable research has been completed describing the effects of various hypotensive techniques on cerebral perfusion, few investigations have dealt with regional myocardial blood flow.

Most coronary vasodilators increase flow equally in the subepicardium and subendocardium, but ATP is unusual in that it preferentially increases flow to the subendocardium, resulting in an increase in the subendocardial-to-subepicardial flow ratio (endo/epi) (2). Recently, ATP has also been found to produce endothelium-dependent relaxation of precontracted isolated blood vessels mediated through a release of endothelium-derived relaxing factor (EDRF) (3). In contrast, sodium nitroprusside produces endothelium-independent relaxation of isolated blood vessels (4). The present investigation was designed to examine the relation between the distribution of increased myocardial perfusion and the in vivo release of EDRF. Direct effects of the vasodilators on myocardial blood flow without confounding changes in systemic hemodynamics were produced by intracoronary drug administration. The actions of the endothelium-dependent vasodilator, ATP, were compared to those of the endothelium-independent vasodilator, sodium nitroprusside, before and after administration of quinacrine (a phospholipase A_2 inhibitor), which blocks the formation and/or release of EDRF (5).

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Materials and Methods

General Preparation

Approval for animal use in this study was granted by the Animal Care Committee of the Medical College of Wisconsin. Fasting adult mongrel dogs of either sex, weighing 15 to 25 kg, were anesthetized with pentobarbital sodium (30 mg/kg supplemented with 5 $mg \cdot kg^{-1} \cdot hr^{-1}$, IV) and ventilated by a respirator (Harvard model 607) with room air enriched with O_2 (0.5–1.0 L/min) at 10–15 breaths/min. Atelectasis was prevented by maintaining an expiratory pressure of 5–7 cm water with a trap. Arterial blood pH was maintained between 7.35 and 7.45 by adjustment of the respiratory rate and by IV infusion of 1.5% sodium bicarbonate when necessary. Rectal temperature was monitored and maintained at 37.5 ± 1°C by a heating pad and servomechanical controller.

Mean arterial blood pressure was recorded using a pressure transducer-tipped catheter (Millar PC380; 8F) inserted into the right femoral artery and advanced to the thoracic aorta. The right femoral vein and left femoral artery were catheterized for drug administration and for withdrawal of reference arterial blood samples used in determining myocardial tissue blood flow, respectively. Left ventricular systolic and end-diastolic pressures were measured by means of another pressure transducer-tipped catheter (Millar PC380; 8F) passed via the left carotid artery into the left ventricle. Peak positive dP/dt, an index of left ventricular global contractility, was obtained by electronic differentiation of the left ventricular pressure pulse. A triangular wave signal of known slope was used to calibrate the differentiator.

Thoracotomy was performed at the left fifth intercostal space. The lung was retracted and the heart suspended in a pericardial cradle. A distal segment of a small-diameter diagonal branch of the left anterior descending coronary artery was dissected from surrounding tissue and cannulated with a heparin-filled catheter (PE-60) for intracoronary drug infusions. The tip of the catheter was advanced to the origin of the branch at the left anterior descending coronary artery to avoid any trauma to the endothelium of the main coronary artery. A 1.0- to 1.5-cm segment of the left anterior descending coronary artery was carefully dissected from surrounding tissue distal to the cannulated branch, and an electromagnetic flow probe (Statham 7515) was placed around the vessel for measurement of coronary blood flow. A silk ligature distal to the flow probe was used to occlude the vessel to establish zero flow, and the probe was calibrated with blood at the completion of each experiment. Preparations were not considered acceptable unless at least a doubling of flow occurred during the reactive hyperemic response after a 20-second total coronary artery occlusion.

A catheter was placed in the left atrium via the atrial appendage for the injection of tracer microspheres. Heart rate was determined from the ECG (limb lead II). The ECG, phasic, and mean aortic and left ventricular systolic and end-diastolic pressures, peak positive dP/dt, and phasic and mean coronary blood flows were continuously recorded on a polygraph (Grass model 7).

Regional Myocardial Blood Flow

The distribution of coronary blood flow was determined by the radioactive microsphere technique (6). Carbonized plastic microspheres (15 ± 3 μm diameter, New England Nuclear) labeled with either ^{141}Ce, ^{51}Cr, ^{103}Ru, or ^{95}Nb were obtained as 2 mCi nuclide in 10 ml of isotonic saline to which 1 drop of Tween 80 was added to minimize aggregation. Before the left atrial injection, the mixture was vigorously agitated. A timed collection of reference flow from the femoral artery was started immediately before injection and maintained at a constant rate (7 ml/min) for 3 minutes. Approximately 2–4 × 10^6 microspheres were injected into the left atrium in a volume of 0.8 to 1.0 ml and flushed in with 4–6 ml of normal saline.

After completion of the experiment, India ink was injected intracoronary through the diagonal branch catheter at mean aortic pressure to stain the area of myocardium exposed to intracoronary drug infusions. The heart was fibrillated by electronic stimulation, excised, washed with saline, and fixed in 10% formaldehyde solution for 24 to 48 hours. After removal of the right ventricular free wall, septum, valves, atria, epicardial fat, and blood vessels, the left ventricle was sectioned into normal (unstained) and drug-perfused (stained) regions. Care was taken to avoid any partially stained or border pieces. Each tissue sample was subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal weight (0.5 to 1.0 g). The samples were weighed, placed in glass scintillation vials, and the activity of each isotope was determined in duplicate at four energy windows in an Autogamma spectrometer equipped with a dual-channel analyzer (Searle Analytic 1195). Similarly, the activity of each isotope in the reference blood flow samples was also determined. The true activity of each isotope in the tissue sample was calculated by correcting for energy overlap. Myocardial blood flow (Q_m; $ml \cdot min^{-1} \cdot g^{-1}$) was calculated from the equation:

$$Q_m = Q_r \cdot C_m / C_r,$$

where Q_r is the rate of withdrawal (ml/min) of the reference blood sample, C_r is the true activity (counts/min) of the reference blood sample, and C_m is the activity (counts·min^{-1}·g^{-1}) of the myocardial tissue sample. Myocardial blood flow of tissue samples from the stained (drug-perfused) and unstained (normal) areas were pooled for calculation of flow in the subepicardium, midmyocardium, and subendocardium of both regions. Transmural myocardial blood flow was the weighted average of flows in the subepicardium, midmyocardium, and subendocardium in drug-perfused or normal zones.

Experimental Design

After completion of surgery, sotalol 2.0 mg/kg, IV was administered to block myocardial and coronary vascular β—adrenoceptors as previously described (7). After a 30-minute equilibration period, the peak reactive hyperemic response after a 20-second total left anterior descending coronary artery occlusion was obtained. In 17 dogs after β-adrenergic blockade, mean coronary blood flow during reactive hyperemia was increased from 17 ± 2 to 56 ± 7 ml/min. This information allowed selection of a dose of drug to be administered via intracoronary infusion that produced submaximal vasodilation of the left anterior descending perfusion territory to avoid nonspecific changes in the transmural distribution of coronary flow that occur during maximal vasodilation (8). In addition, intracoronary infusion permitted study of the direct effects of the vasodilators on myocardial blood flow independent of peripheral hemodynamic actions.

The endothelium-dependent vasodilator, ATP, was administered intracoronary at 10, 20, and 50 μg/min and compared with sodium nitroprusside (20, 40, and 90 μg/min), a non-endothelium–dependent vasodilator. The influence of the phospholipase A_2 inhibitor quinacrine (300 μg/min, IC), which blocks the release of EDRF, on the actions of the vasodilator agents was also determined. Separate groups of dogs (N = 9 and 8) were used to study ATP and sodium nitroprusside, respectively. In each experiment, the first radioactive microsphere was administered during intracoronary vehicle infusion (control state). Each vasodilator was then infused into coronary arteries in increasing doses for 5 minutes to establish a dose–response relation for coronary blood flow. Subsequently, the second microsphere was administered at steady-state flow conditions during a 5-minute intracoronary infusion of a dose of each vasodilator that produced an increase in coronary blood flow that was 50–75% of the peak reactive hyperemic response. The third radioactive microsphere was injected at the end of a 30-minute intracoronary infusion of quinacrine (300 μg/min) to assess any direct effects of the phospholipase A_2 inhibitor on regional myocardial perfusion. Each vasodilator was again infused into coronary arteries in the doses established before quinacrine administration. The fourth radioactive microsphere was then administered in the presence of quinacrine at steady-state flow conditions during vasodilator infusion at the same dose as used for the second microsphere.

All drugs were freshly prepared on the day of the experiment. Sotalol, ATP, quinacrine, and sodium nitroprusside were dissolved in 0.9% sodium chloride solution. Care was taken to avoid contact of the sodium nitroprusside solution with light. Syringes and tubing were covered, and these experiments were performed under light emitted from a sodium vapor lamp.

Statistical Analysis

All values are reported as mean ± SEM. Analysis of variance within a randomized complete block design with four treatments was used to test of main effects (9). Simple effects were examined with the Waller–Duncan adaptive multiple comparisons procedure (10). Probability values of <0.05 were considered statistically significant.

Results

Hemodynamics

Hemodynamic data after intracoronary infusion of ATP (20 μg/min) and sodium nitroprusside (40 μg/min) are summarized in Tables 1 and 2, respectively. Neither compound produced significant changes in heart rate, left ventricular and aortic pressures, or peak positive dP/dt. In contrast, both ATP and nitroprusside produced significant ($P < 0.05$) increases in total coronary blood flow of the drug-perfused region that were equal to 58 and 62% of the peak reactive hyperemic response, respectively. Peak diastolic coronary blood flow was significantly increased by both compounds, whereas systolic coronary blood flow was increased only by sodium nitroprusside.

Intracoronary infusion of quinacrine (300 μg/min) had no significant effect on heart rate, left ventricular

Table 1. Effects of ATP (20 μg/min) on Hemodynamics before and after Quinacrine (300 μg/min)

	Control	ATP	Quinacrine	Quinacrine + ATP
Heart rate (beats/min)	112 ± 5*	113 ± 5	116 ± 4	117 ± 4
Mean aortic blood pressure (mm Hg)	95 ± 6	94 ± 5	89 ± 8	87 ± 9
Left ventricular systolic pressure (mm Hg)	116 ± 7	114 ± 7	109 ± 8	108 ± 9
Left ventricular end diastolic pressure (mm Hg)	4 ± 1	4 ± 1	5 ± 1	5 ± 1
Peak positive dP/dt (mm Hg/sec)	1950 ± 125	1900 ± 125	1450 ± 150†	1625 ± 100†
Mean coronary blood flow (ml/min)	11 ± 2	24 ± 3†	12 ± 2	16 ± 1†
Systolic coronary blood flow (ml/min)	3 ± 2	11 ± 2†	4 ± 2	9 ± 3
Diastolic coronary blood flow (ml/min)	18 ± 2	46 ± 3†	21 ± 4	33 ± 4†,‡

*Values are the mean ± SEM (n = 9).
†Significant difference from control ($P < 0.05$).
‡Significant difference from quinacrine ($P < 0.05$).

Table 2. Effects of Sodium Nitroprusside Infusion (40 μg/min) on Hemodynamics before and after Quinacrine (300 μg/min)

	Control	Nitroprusside	Quinacrine	Quinacrine + nitroprusside
Heart rate (beats/min)	132 ± 4*	131 ± 4	135 ± 6	137 ± 7
Mean aortic blood pressure (mm Hg)	98 ± 5	91 ± 5	96 ± 5	91 ± 7
Left ventricular systolic pressure (mm Hg)	117 ± 7	112 ± 8	115 ± 6	111 ± 8
Left ventricular end diastolic pressure (mm Hg)	5 ± 3	3 ± 2	3 ± 1	4 ± 2
Peak positive dP/dt (mm Hg/sec)	1600 ± 200	1500 ± 200	1325 ± 125†	1225 ± 100†
Mean coronary blood flow (ml/min)	23 ± 2	39 ± 5†	19 ± 2	31 ± 5†,‡
Systolic coronary blood flow (ml/min)	3 ± 2	11 ± 3†	2 ± 1	4 ± 2
Diastolic coronary blood flow (ml/min)	41 ± 3	70 ± 8†	33 ± 4†	59 ± 10†,‡

*Values are the mean ± SEM (n = 8).
†Significant difference from control ($P < 0.05$).
‡Significant difference from quinacrine ($P < 0.05$).

and aortic pressures, or coronary blood flow. Coronary blood flow was slightly increased in the ATP series and decreased in the nitroprusside series, although these changes were not significant. Peak positive dP/dt was reduced after quinacrine infusion. The peak reactive hyperemic response to a 20-second total coronary artery occlusion was unchanged by quinacrine. In 17 dogs, mean coronary blood flow increased from 17 ± 2 to 56 ± 7 ml/min before and 15 ± 2 to 50 ± 5 ml/min after quinacrine.

Regional Myocardial Perfusion

Blood flow to the subepicardium, midmyocardium, subendocardium, and the average transmural blood flow of the normal (left circumflex) and drug-perfused (left anterior descending) regions are summarized in Tables 3 and 4. Intracoronary infusion of ATP (20 μg/min) or sodium nitroprusside (40 μg/min) had no effect on tissue flow in the non-drug–perfused region. In contrast, both compounds produced significant increases in transmural blood flow in the drug-perfused region. The transmural distribution of flow across the left ventricular free wall produced by ATP preferentially favored the subendocardium, thus increasing the ratio of subendocardial to subepicardial flow (endo/epi) (Fig. 1). Endo/epi remained unchanged in the presence of sodium nitroprusside despite significant increases in transmural flow (Fig. 1, Table 4).

Quinacrine produced a nearly equivalent decrease in subepicardial, midmyocardial, subendocardial, transmural, or diastolic coronary blood flow in the drug-perfused region of nitroprusside-treated dogs. However, this only reached statistical significance for the measurement of diastolic coronary blood flow. In contrast, there was no significant change in blood flow in the ATP-treated group although there was a trend to increased flow (Tables 3 and 4). Likewise, quinacrine produced no change in endo/epi (Fig. 1). Whereas the absolute increase in overall tissue perfusion was unaffected (Table 1), the preferential redistribution of blood flow to the subendocardium produced by ATP was prevented by quinacrine infusion (Fig. 1). In contrast, the increase in transmural flow produced by sodium nitroprusside was unchanged and no redistribution of flow occurred with quinacrine plus sodium nitroprusside.

Table 3. Effects of ATP (20 μg/min) on Regional Myocardial Blood Flow (ml/min/g) before and after Quinacrine (300 μg/min)

	Control	ATP	Quinacrine	Quinacrine + ATP
Normal region				
Subepicardium	0.72 ± 0.09*	0.80 ± 0.13	0.86 ± 0.16	0.80 ± 0.10
Midmyocardium	0.79 ± 0.09	0.92 ± 0.12	0.94 ± 0.14	0.96 ± 0.15
Subendocardium	0.84 ± 0.08	0.97 ± 0.10	0.92 ± 0.11	0.90 ± 0.13
Transmural	0.78 ± 0.08	0.90 ± 0.11	0.91 ± 0.13	0.89 ± 0.13
Drug-perfused region				
Subepicardium	0.73 ± 0.11	1.31 ± 0.19†	0.98 ± 0.23	1.20 ± 0.23
Midmyocardium	0.75 ± 0.10	1.97 ± 0.26†	1.01 ± 0.23	1.44 ± 0.26
Subendocardium	0.79 ± 0.11	2.44 ± 0.29†	1.05 ± 0.24	1.58 ± 0.27†
Transmural	0.76 ± 0.10	1.91 ± 0.24†	1.01 ± 0.22	1.40 ± 0.24†

*Values are the mean ± SEM (n = 9).
†Significant difference from control ($P < 0.05$).

Table 4. Effects of Sodium Nitroprusside (40 μg/min) on Regional Myocardial Blood Flow (ml/min/g) before and after Quinacrine (300 μg/min)

	Control	Nitroprusside	Quinacrine	Quinacrine + nitroprusside
Normal region				
Subepicardium	0.64 ± 0.07*	0.58 ± 0.04	0.65 ± 0.06	0.70 ± 0.07
Midmyocardium	0.78 ± 0.08	0.74 ± 0.08	0.85 ± 0.10	0.87 ± 0.11
Subendocardium	0.95 ± 0.11	0.97 ± 0.15	0.93 ± 0.11	0.97 ± 0.11
Transmural	0.79 ± 0.10	0.76 ± 0.12	0.81 ± 0.09	0.85 ± 0.10
Drug-perfused region				
Subepicardium	0.89 ± 0.13	1.77 ± 0.22†	0.59 ± 0.08	1.15 ± 0.20
Midmyocardium	0.83 ± 0.09	1.87 ± 0.21†	0.55 ± 0.07	1.32 ± 0.23
Subendocardium	0.99 ± 0.16	2.07 ± 0.30†	0.63 ± 0.07	1.45 ± 0.24†
Transmural	0.93 ± 0.16	1.90 ± 0.27†	0.59 ± 0.07	1.31 ± 0.21†

*Values are the mean ± SEM (n = 8).
†Significant difference from control ($P < 0.05$).

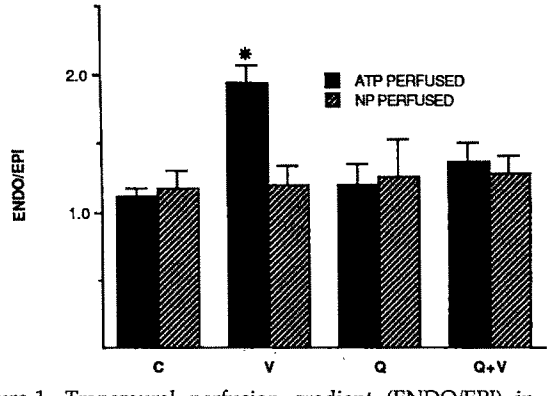

Figure 1. Transmural perfusion gradient (ENDO/EPI) in drug-perfused region during control (C; vehicle infusion), vasodilator infusion (V), quinacrine infusion (Q; 300 μg/min, IC), and quinacrine plus vasodilator (Q + V). Vasodilators are adenosine triphosphate (ATP; 20 μg/min, IC) and sodium nitroprusside (NP; 40 μg/min, IC) *Significant ($P < 0.05$) difference from control.

Discussion

The purpose of the present study was to characterize the effects of two hypotensive agents on regional coronary blood flow. The endothelium-dependent vasodilator, ATP, was compared to the endothelium-independent vasodilator, sodium nitroprusside. Quinacrine was used to inhibit phospholipase A_2 and block the release and/or formation of EDRF. The effects of phospholipase A_2 inhibition on the vasodilation produced by these compounds were also investigated. The results demonstrate that the endothelium-dependent compound, ATP, produces a preferential increase in subendocardial perfusion, thus increasing the subendocardial-to-subepicardial blood flow ratio, whereas endo/epi was unchanged by sodium nitroprusside. Blockade of the ATP-mediated flow redistribution by quinacrine suggests that the increased endo/epi is mediated by EDRF, which may be a product of unsaturated fatty acid metabolism.

Several endothelium-dependent vasodilators, including acetylcholine and histamine, preferentially increase subendocardial blood flow after intracoronary administration due to a direct dilator action on the subendocardial vasculature (11,12). ATP, another

endothelium-dependent vasodilator (3), increases endo/epi after IV administration during aortic cross-clamping distal to the left subclavian artery when compared to flow measured during cross-clamping alone (2). In addition, IV infusion of ATP produces large increases in myocardial blood flow, whereas an equal hypotensive dose of sodium nitroprusside produces no significant change in myocardial blood flow but greatly increased skeletal muscle perfusion in rats (13). In the present study, increases in endo/epi as well as transmural perfusion were observed due to the direct effects of ATP on myocardial blood flow in the absence of systemic hemodynamic changes. However, intracoronary infusion of sodium nitroprusside, an endothelium-independent hypotensive agent, produced increases in transmural myocardial blood flow without altering the subendocardial-to-subepicardial flow ratio.

Coronary blood flow measured during control (vehicle infusion) was higher in the nitroprusside-treated group than in the ATP-treated group. However, regional myocardial blood flow and flow distribution (endo/epi) measured with microspheres was not different between the two groups. This could reflect a difference in the sizes of the drug-perfused regions. In addition, myocardial vasodilator reserve was similar between groups because the reactive hyperemic response to a 20-second coronary artery occlusion was equal, indicating that the differences in resting coronary blood flow are not important in assessing vasodilator responses.

In the present study, no readily identifiable hemodynamic factors capable of altering endo/epi, such as myocardial contractility, diastolic perfusion time or coronary perfusion pressure, were changed by intracoronary vasodilator administration. Thus, the preferential increase in subendocardial blood flow produced by ATP is not accounted for by hemodynamic changes. Quinacrine produced a decrease in peak positive dP/dt in all dogs but had no other effects on hemodynamics. Quinacrine infusion in the presence of ATP or sodium nitroprusside also produced decreases in global contractility. Gross et al. (14) have previously demonstrated contractility to have only minimal effects on endo/epi provided left ventricular pressures were unchanged, as in this study. Thus, the observed changes in contractility would not be expected to influence the redistribution of blood flow produced by ATP. Furthermore, the regional distribution of increased blood flow produced by sodium nitroprusside was unchanged after quinacrine.

Quinacrine infusion had no significant effect on coronary blood flow or regional myocardial perfusion. However, transmural blood flow in the sodium nitroprusside-treated dogs tended to decrease after quinacrine administration. Whereas absolute coronary blood flow after sodium nitroprusside infusion was less after quinacrine administration, the change in flow was the same. Part of the absolute flow reduction may be accounted for by the negative inotropic actions of quinacrine as well as tachyphylaxis to sodium nitroprusside (13).

Activation of phospholipases and subsequent release of arachidonic or other unsaturated fatty acids and metabolism by lipoxygenase or cytochrome P-450 may be the basis for endothelial-dependent relaxations (3,15). Unsaturated fatty acids, hydroxyl free radicals, and lipid peroxides, products of these enzyme systems, have all been shown to activate guanylate cyclase directly (16) causing vasodilation via cyclic GMP, the final mediator of endothelium-dependent vasodilation. Thus, these compounds have been suggested as possible candidates for EDRF. Quinacrine, a phospholipase A_2 inhibitor (17), has previously been shown to block endothelium-dependent relaxations produced by acetylcholine and ATP (6) in rabbit aorta, but not those produced by ATP in the canine femoral artery (18). The basis for these results may be related to either species differences or altered reactivities of various vascular beds. In the present study, quinacrine infusion alone had no effect on regional myocardial perfusion but blocked the redistribution of coronary blood flow to the subendocardium produced by ATP. However, quinacrine infusion did not affect transmural increases in flow produced by either compound. These results suggest that ATP and nitroprusside increase total coronary blood flow by a mechanism that is independent of EDRF, but the selective redistribution of flow to the subendocardium produced by ATP is dependent on formation of EDRF.

The vasodilators investigated in the present study increase myocardial blood flow directly; however, ATP has the potential to preferentially increase subendocardial perfusion. In addition, undesirable side effects of sodium nitroprusside, such as cyanide toxicity and tachyphylaxis, are not associated with the use of ATP (13). Thus, ATP may ultimately be a useful agent for producing controlled hypotension during anesthesia.

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Continuous Electromyography for Monitoring Depth of Anesthesia

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Utilizing a randomized, controlled study design, the clinical utility of monitoring spontaneous electromyography during methohexital anesthesia was evaluated for short outpatient gynecologic procedures. In the experimental group (n = 20), the anesthesiologist used conventional monitors as well as the Datex ABM device for determining the maintenance anesthetic requirement. The control group (n = 20) was monitored in an identical fashion, but the video monitor screen was turned off during the operation. The methohexital maintenance requirement was nonsignificantly decreased (5.0 ± 1.2 vs 5.6 ± 1.8 mg/min) in the experimental group. Adequacy of anesthesia (as determined by cardiorespiratory stability and the absence of purposeful movement during the maintenance period) did not differ between the two study groups. Although the awakening time for the experimental group (2.9 ± 1.9 minutes) was decreased to a statistically significant degree compared to the control group (4.5 ± 3.0 minutes), the difference was of no clinical significance. Thus, continuous electromyographic and EEG monitoring with the Datex ABM device did not significantly improve administration of methohexital during brief outpatient procedures.

Key Words: ANESTHESIA—depth. ANESTHETICS, INTRAVENOUS—thiopental, methohexital. MEASUREMENT TECHNIQUES—electromyography, electroencephalography.

A reliable, noninvasive monitor of depth of anesthesia could increase the precision involved in determining anesthetic and analgesic dosage requirements. Improvement in our ability to administer anesthetics would decrease the incidence of side effects both during and after the operative procedure. Theoretically, more precise techniques for administering centrally active drugs during ambulatory (outpatient) anesthesia might also contribute to a more rapid recovery after surgery.

The Datex Anesthesia and Brain Monitor (ABM) is a device that can be used to continuously record electromyographic (EMG) and electroencephalographic (EEG) activity during anesthesia (1,2). Harmel et al. (3) suggested that "electroencephalomyogram" activity recorded from the frontalis muscle region could be useful in defining "an adequate state of surgical relaxation." Sudden increases in the amplitude of spontaneous frontalis muscle EMG activity during an operation were alleged to indicate enhanced patient responsiveness (4). Previous studies have also demonstrated that the EEG can be a sensitive measure of residual anesthetic effects and might be useful in assessing recovery after outpatient anesthesia (5,6).

This clinical study was designed to ascertain if the use of the ABM device could improve the anesthesiologists' ability to use a methohexital infusion for maintenance of anesthesia as an adjuvant to nitrous oxide during outpatient anesthesia.

Materials and Methods

Forty healthy (ASA physical status I) young women scheduled for elective outpatient gynecologic procedures (e.g., dilatation and extraction) were randomly assigned to one of two treatment groups. Patients in group I (control) were monitored with conventional monitors as well as the ABM device, but the ABM video monitor screen was turned off during the operation. In group II (experimental), the patients were monitored in an identical fashion, but the

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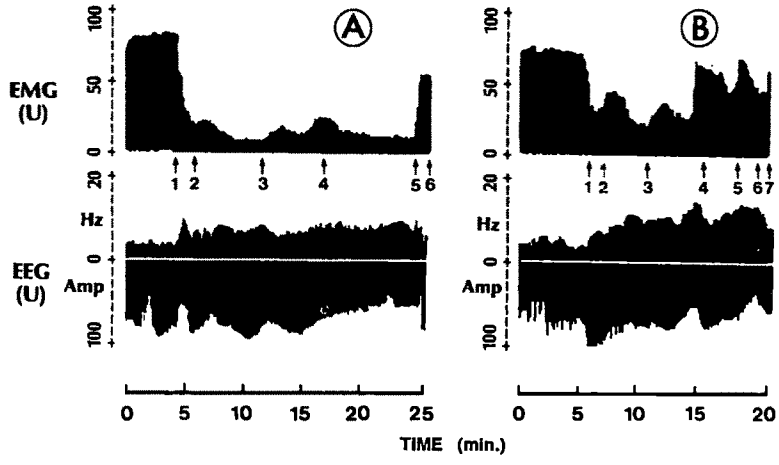

Figure 1. (A), EMG and EEG activity patterns in an adequately anesthetized patient with no movement or acute cardiorespiratory changes during the operation. Key events: 1, thiopental, 4 mg/kg IV; 2, surgical preparation; 3, start surgery; 4, maximum stimulation; 5, discontinued N_2O and; 6, awakening. (B) EMG and EEG activity patterns in a patient who moved twice in response to surgical stimulation and manifested significant increases in both heart rate and respiratory rate during the operation. Key events: 1, thiopental; 4 mg/kg IV; 2, surgical preparation; 3, start surgery; 4, purposeful movement; 5, purposeful movement; 6, discontinued N_2O and; 7, awakening.

anesthesiologist was allowed to utilize the information displayed on the video monitor screen to determine when to give additional anesthetic medication during the maintenance period. The protocol was approved by the local institutional review board and written informed consent was obtained from each patient. The operation of the ABM device was explained to the four anesthesiologists who participated in the study. Each anesthesiologist performed ten study cases (five in each treatment group) using the same general anesthetic technique. The same gynecologic surgeon (WAD) performed all the operative procedures.

These unpremedicated outpatients were taken to the operating room where an 18-gauge IV catheter was inserted into a forearm vein. Conventional monitoring devices consisted of an ECG, Dinamap blood pressure cuff, Nellcor pulse oximeter, and a precordial stethoscope. After using an alcohol wipe and a dry gauze sponge to prepare the skin, disposable cutaneous silver/silver chloride ECG electrodes were placed at the midforehead, temple and mastoid regions to record spontaneous EMG and EEG activity. End-tidal carbon dioxide concentrations ($P_{ET_{CO_2}}$) and respiratory rate (RR) were monitored using a Puritan-Bennett capnograph connected to the rebreathing circuit at the "Y" connector adjacent to the face mask. Heart rate (HR), mean arterial pressure (MAP), $P_{ET_{CO_2}}$, and RR were recorded at 1- to 2-minute intervals.

All patients received droperidol 0.5 mg IV and meperidine 1 mg/kg IV 3–5 minutes before the induction of anesthesia. Anesthesia was induced with thiopental 4 mg/kg IV over 30–60 seconds, and when the patient became unresponsive (i.e., loss of response to verbal commands), nitrous oxide (N_2O) 70% in oxygen (7:3 L/min) was administered via a tight-fitting face mask using a conventional circle absorber system. A methohexital infusion (2 mg/ml) was started at an initial infusion rate of 4 mg/min to supplement nitrous oxide. An attempt was made to maintain a stable level of anesthesia by varying the rate of the methohexital infusion in response to clinical signs of inadequate anesthesia (e.g., movement, increases in RR, HR, and MAP) or excessive drug effect (e.g., decreases in MAP, HR, or RR). Purposeful movement was treated by administering a small bolus dose of methohexital, 5–10 mg IV, and increasing the maintenance infusion rate. The maintenance anesthetic requirement was determined by dividing the total amount of methohexital administered by the duration of anesthesia.

The Datex ABM monitor displayed numerical values of frontalis muscle EMG activity, frontal EEG amplitude and zero crossing frequency, as well as a bar graph of spontaneous EMG and EEG activity versus time (Fig. 1). The EMG input signal was processed through a 65- to 400-Hz band-pass filter before being digitized and displayed as a bar graph on the video monitor. A hard copy of the bar graph plot was obtained for each patient using an Epson MTX 80-dot matrix printer (7). An event marker was used to temporally identify events during the perioperative period.

EMG values were recorded at the following times: 1) 1–3 minutes before induction of anesthesia (baseline), 2) 2 minutes after induction with thiopental, 3) maximum value during surgical preparation, 4) immediately before initiation of surgical stimulation, 5) maximum value during the operation, 6) at the time surgical stimulation ended and the methohexital infusion was discontinued, 7) at the time N_2O was stopped and, 8) 2 minutes after N_2O was discontinued. Changes in EMG values were determined after induction of anesthesia [1) − 2)], surgical preparation [3) − 2)], surgical stimulation [5) − 4)], and discontinuation of N_2O [8) − 7)]. Minimum and maximum

Table 1. Demographic and Anesthetic Data for the Two Study Groups*

Variable	Control	Experimental
Number (*n*)	20	20
Age (yr)	27 ± 9	24 ± 8
Weight (kg)	64 ± 9	58 ± 9
Preinduction MAP (mm Hg)	90 ± 9	92 ± 10
Preinduction HR (beats/min)	80 ± 10	78 ± 9
Preinduction RR (beats/min)	17 ± 2	16 ± 2
Duration of anesthesia (min)	21 ± 4	22 ± 5
Mean infusion rate (mg/min)	5.6 ± 1.8	5.0 ± 1.2
Awakening time (min)	4.5 ± 3.0	2.9 ± 1.9†

*Mean values ± SD.
†Significantly different from the control group, $P < 0.05$.

Pco_2 values were recorded as well as the averaged Pco_2 value during the operation.

Adequacy of induction was defined as loss of consciousness within 30–60 seconds after injecting thiopental, without purposeful movements. Adequate anesthesia during surgical preparation (before surgical stimulus) and the operation itself was defined as the presence of stable levels of MAP, HR, and RR (within 20% of the postinduction values) and the absence of purposeful movement. The time to awakening was defined as the time interval between discontinuation of N_2O and the ability of the patient to respond to a verbal command to open her eyes.

Data were analyzed as follows: 1) Continuous variables were analyzed using analysis of variance with Kruskal–Wallis and Wilcoxon tests and; 2) discrete variables were analyzed using χ^2 tests, with P values <0.05 considered statistically significant. Data are presented as mean values ± SD.

Results

The two study groups were comparable with respect to demographic data and baseline cardiovascular and respiratory variables (Table 1). The mean maintenance infusion rate for methohexital was decreased by a statistically nonsignificant 12% in the experimental group in which the ABM monitor was utilized during the operation. Adequacy of anesthesia, as determined by cardiorespiratory stability and the absence of purposeful movement during the maintenance period, was not significantly different between the two study groups. Furthermore, the EMG values showed no significant differences at comparable time points during administration of the maintenance anesthetic (Table 2). Although awakening time in the experimental group was statistically significantly shorter than that in the control group (Table 1), this difference was not clinically significant.

Table 2. Electromyographic (EMG) Values during the Perioperative Period in Control and EMG Monitored (Experimental) Groups*

EMG value	Control	Experimental
Preoperative baseline	70 ± 8	68 ± 7
After induction of anesthesia	37 ± 10	40 ± 12
Before surgical stimulation	29 ± 16	31 ± 15
Maximal surgical stimulation	50 ± 21	52 ± 23
Methohexital infusion discontinued	44 ± 21	48 ± 21
N_2O discontinued	40 ± 43	47 ± 38
2 minutes after N_2O discontinued	47 ± 51	56 ± 27

*Mean values ± SD.

Table 3. Comparative Electromyographic (EMG) and End-Tital Carbon Dioxide ($P_{ET}CO_2$) Values for Patients Adequately and Inadequately Anesthetized*

	Adequate	Inadequate*
EMG Values		
Preinduction (baseline)	63 ± 9	64 ± 12
After induction of anesthesia	37 ± 13	52 ± 22
Before surgical preparation	27 ± 15	28 ± 20
During surgical preparation	33 ± 17	42 ± 18‡
Before surgical stimulation	30 ± 16	29 ± 15
Maximal surgical stimulation	46 ± 18	68 ± 16‡
$P_{ET}co_2$ values		
Mean intraoperative	34.3 ± 6.4	32.4 ± 2.5
Change during surgery	−4.9 ± 3.2	−5.8 ± 3.9

*Criteria for inadequacy included purposeful movements or changes in cardiorespiratory parameters exceeding 20% of the postinduction values (see Materials and Methods).
†Mean values ± SD.
‡Significantly different from adequate group, $P < 0.05$.

Table 4. Relation between Electromyographic (EMG) Values and Awakening Times after Anesthesia*

	Rapid awakening (≤5 minutes)	Slow awakening (>5 minutes)
EMG values		
Preoperative baseline	63 ± 8 (43–78)	62 ± 16 (34–85)
Discontinued infusion	48 ± 20 (16–80)	31 ± 20† (15–63)
Discontinued N_2O	46 ± 18 (19–75)	29 ± 17† (17–58)
2 minutes after N_2O discontinued	65 ± 18 (25–86)	32 ± 16‡ (17–52)

*Mean values ± SD (range of values).
†Significantly different from rapid awakening, $P < 0.10$.
‡Significantly different from rapid awakening, $P < 0.05$.

Combining data obtained from both study groups, the EMG values were evaluated in both adequately (75%) and inadequately (25%) anesthetized patients as a monitor of anesthetic depth and as a predictor of awakening time (Tables 3 and 4). Comparable baseline (preinduction) EMG values were recorded in both patient groups. At 2 minutes after induction, however, the decrease in the EMG was significantly less in patients inadequately induced (8 ± 5 U) than

in those who were adequately induced (26 ± 11 U). Compared to adequately anesthetized patients, those who moved during the preparation period displayed significantly greater changes in EMG values in response to this stimulus (13 ± 6 vs 6 ± 3 U, respectively). Furthermore, the maximum change in the EMG value during the operation was also significantly greater for patients who moved (39 ± 8 U) than for those who did not move (16 ± 10 U). Only 29% of the patients considered adequately anesthetized displayed a change in the EMG exceeding 30 U (vs 56% of those inadequately anesthetized). The percentage change in the EMG with surgical stimulation (relative to the presurgery values) was also significantly greater in patients who moved during surgery (175%) than in nonmoving patients (72%).

End-tidal carbon dioxide ($P_{ET_{CO_2}}$) values recorded during surgery showed no significant differences in averaged $P_{ET_{CO_2}}$ values or the maximum $P_{ET_{CO_2}}$ change between the control and experimental study groups. Although the averaged $P_{ET_{CO_2}}$ value was lower in the inadequately anesthetized group (Table 3), the difference was not statistically significant. EMG values at the end of the operation were consistently higher in patients who awoke within 5 minutes of discontinuing N_2O than in patients with delayed emergence (>5 minutes) (Table 4). In addition, the increase in the EMG 2 minutes after discontinuing N_2O was significantly higher in the rapidly awakening group ($P < 0.05$).

Examples of the EMG and EEG changes for an adequately and inadequately anesthetized patient are shown in Figure 1. Using the EEG recordings generated by the ABM device, we were unable to correlate changes in the compressed frontal EEG amplitude (or frequency) with hemodynamic, respiratory, or somatic signs of depth of anesthesia.

Discussion

A noninvasive depth of anesthesia monitor would be of clinical value if it improved the anesthesiologist's ability to administer anesthetic drugs during the maintenance periods. The ABM monitor allows the anesthesiologist to continuously monitor EMG and EEG activity as well as $P_{ET_{CO_2}}$ values. Compared to a study group anesthetized without the aid of this monitoring device, there was no significant difference in the incidence of movement between the two groups (22–29%). The decrease time to awakening for the group with ABM monitoring might suggest improved titration of the maintenance anesthetic, as evidenced by a 12% decrease in the methohexital infusion rate.

As expected, the largest changes in the EMG were observed when patients moved in response to the surgical stimulus (Fig. 1). In comparing the adequately and inadequately anesthetized patients (Table 3), significant differences in EMG values were present. Unfortunately, the EMG changes often occurred 5–10 seconds after the patient moved and were therefore of limited predictive value in adjusting the maintenance infusion. Although a patient with a higher EMG value was more likely to move, the absolute EMG value was not a reliable indicator of depth of anesthesia. Furthermore, large increases in EMG values during the operation were found in patients who did and did not move in response to the surgical stimulus. Notably, none of the patients with a decrease in EMG activity during surgical stimulation moved. Thus, decreasing EMG activity during an operation may indicate an increasing depth of anesthesia. Increases in EMG activity during the operation were usually associated with decreases in end-tidal P_{CO_2} values. Clinically, changes in respiratory rate were a more useful measure of anesthetic depth because these changes occurred 15–30 seconds before changes in EMG activity were noted.

This preliminary study suggests that monitoring spontaneous EMG and EEG activity is of limited clinical value in assessing depth of anesthesia during short outpatient operations when intravenous anesthetics and nitrous oxide are used. This monitor might be of greater value when used during longer operations or in the presence of inhaled (volatile) anesthetics. Because only one type of EMG–EEG monitor was evaluated, it is possible that other monitors may be more sensitive to the changes produced by surgical stimulation. Furthermore, the position of the EMG–EEG recording electrodes could affect the amplitude of the spontaneous EMG–EEG activity.

Use of a more elaborate skin preparation (e.g., Omniprep) before applying the cutaneous gel electrodes would probably increase the sensitivity of the monitor and decrease interpatient variability. Another limitation of our study design relates to the use of subjective (clinical) criteria to assess the depth of anesthesia and to make adjustments in the maintenance infusion rate. Interestingly, other investigators (8) have reported that increases in EMG activity occur after presentation of acoustic stimuli to patients during "deep surgical anesthesia." Thus, EMG changes unrelated to surgical stimulation can complicate interpretation of these data.

Patients awakening within 5 minutes of terminating the N_2O had significantly higher EMG values at the end of the operation. These data suggest that EMG data may be of value in predicting awakening

time. Unfortunately, EMG values varied widely among patients, thereby limiting their value in predicting the time to awakening for a particular patient. In conclusion, continuous EMG and EEG monitoring did not significantly improve the titration of intravenous anesthetics used during brief outpatient procedures.

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The Relation Between Lorazepam-Induced Auditory Amnesia and Auditory Evoked Potentials

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SAMRA SK, BRADSHAW EG, PANDIT SK, PAPANICOLAOU AC, MOORE BD. The relationship between lorazepam-induced auditory amnesia and auditory evoked potentials. Anesth Analg 1988;67:526-33.

We conducted a placebo-controlled double-blind investigation in 15 normal volunteers to study the time course of amnesia to auditory stimulation produced by lorazepam. We also studied the relationship between auditory amnesia and auditory evoked potentials to determine if long-latency auditory evoked potentials (LLAEPs) could be utilized as electrophysiologic predictors of memory. Amnesia was produced by administration of 0.05 mg/kg lorazepam intravenously. To separate the changes in LLAEPs due to generalized sedation from those associated with amnestic properties of a drug, a third group of subjects given 1.5 mg/kg secobarbital was included. Observed frequency and duration of amnesia to auditory stimulation after lorazepam was 58% and 3 hours, respectively (mean values), with marked diminuition of antirecall effect at 120 minutes. Administration of lorazepam increased the latency and decreased the amplitude of N_1 and P_3 components of LLAEPs. These changes appeared to be a result of generalized sedation rather than the amnestic properties of the drug. We failed to find a definite relationship between amnesia and changes in LLAEPs. We conclude that P_3 component of LLAEPs cannot be utilized as an electrophysiologic predictor of amnesia in humans.

Key Words: MEMORY—amnesia. BRAIN—auditory evoked potentials. MONITORING—auditory evoked potentials. HEARING—auditory evoked potentials.

The problem of patient awareness during anesthesia has been addressed in several case reports (1–9). Because many of these patients (1–4) were anesthetized with oxygen–nitrous oxide supplemented by narcotics and muscle relaxants, it was recommended that either intravenous drugs such as scopolamine and diazepam or halogenated anesthetics in low concentrations should also be administered to prevent intraoperative awareness. Subsequent studies have reported intraoperative recall despite these adjuvents (5–9). These case reports suggest that a monitoring technique that can predict intraoperative awareness in apparently anesthetized patients will be clinically useful. Moreover, the time course and dose–time–effect relation of the amnesic effect of diazepam and lorazepam, two commonly used premedicants, have been studied in a visual memory paradigm using memory cards showing pictures of familiar objects (10,11). It seems that similar studies using auditory stimulation may be more pertinent to the problem of intraoperative recall.

Evoked potentials are now used clinically as an objective test of sensory function in patients with a variety of neurologic disorders. Evoked potentials consist of two sets of components. The early components are affected by the parameters of evoking stimulation and reflect the integrity of sensory pathway involved. Late components are also affected by cognitive processing of the stimuli (e.g., attention). Among those, P_3, a late positive component of both visual and auditory evoked potentials, appears only when subjects are presented with rare and unpredictable stimuli (12). The latency and amplitude of P_3 are consequently thought to reflect evaluation of the stimuli that is cognitive rather than sensory processes. Evoked potentials after auditory stimulation can be therefore classified as short-latency or brain stem auditory evoked potentials (BAEPs) occurring between 0 and 10 milliseconds, middle-latency

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evoked potentials between 10 and 50 milliseconds, and long-latency auditory evoked potentials (LLAEPs) occurring more than 50 milliseconds after stimulus delivery. BAEPs evaluate the integrity of auditory pathway from the eighth cranial nerve to midbrain (14), whereas LLAEPs are potentials involved with information processing in the brain. Many studies (15–17) have linked the P_3 component of LLAEPs to processes involved in perception and cognition in normal and demented subjects.

We designed this clinical study to evaluate: 1) the time course of auditory amnesia after intravenous injection of lorazepam and, 2) the relation of lorazepam-induced auditory amnesia to changes in P_3 component of LLAEPs.

Methods

Institutional approval of study protocol was obtained. Fifteen healthy paid volunteers with normal hearing (ASA physical status I; 7 males and 8 females) participated in this study. Informed consent was obtained and subjects were randomly assigned to one of the following study groups: group A ($n = 4$) was given a placebo (normal saline), group B ($n = 5$) received 1.5 mg/kg secobarbital, and group C ($n = 6$) was given 0.05 mg/kg lorazepam. Experimental drugs were administered iv in a double-blind manner in equal volumes (2 ml) and the code for various groups was broken at the end of study period after completing all the observations reported in this study.

Subjects reported for the study after an overnight fast. Details of the experimental procedure were explained to each subject. A slow intravenous infusion of lactated Ringer's solution was started. Several variables (objective and subjective) described later were measured at six time points in each subject. These six time points were before administration of drugs (time 0) and 30, 60, 120, 180, and 240 minutes after intravenous injection of one of the three drugs studied. Monitored parameters included blood pressure by an automated blood pressure cuff (Dinamap), ECG (lead II), heart rate, oral temperature, brain stem auditory evoked potentials (BAEPs), and long-latency auditory evoked potentials (LLAEPs). Details of recording techniques for BAEPs and LLAEPs are described later in this paper. In addition to earlier stated objective measurements, the following observations were made by two investigators (SKS and EGB).

Sedation. The level of sedation was graded on a scale of 1–5 as follows: grade 1 = no sedation; grade 2 = calm, but not asleep; grade 3 = asleep, but easily arousable (on being called by name); grade 4 = asleep, but not easily arousable (required touching or shaking); and grade 5 = unable to communicate.

Test for short-term auditory amnesia. At each of the six time points the subject was asked to repeat a randomly assigned three-digit number announced by the observer: immediately (to assure registration) and after 30-second, 2-minute, and 5-minute intervals. A different three-digit number was used at each time of observation. Thus six three-digit numbers were assigned to each subject.

Long-term auditory amnesia. To study retention of information as memory, six common sounds were recorded on audio cassettes called "test tapes." These sounds included a telephone ring, violin, birds chirping, car horn, door bell, and the Christmas song "Jingle Bells." One of these sounds was played for exactly 1 minute at each test interval (specified earlier), and the subject was asked to identify the sound (to assure registration) and remember it for next 24 hours. The order in which these sounds were played was varied at random. Twenty-four hours later the subject was asked to recall all the test sounds he or she had heard the day before. Those who failed to recall any one of the test sounds were asked to identify the six test sounds from a tape recording in which test sounds were intermixed with six "distractor" sounds of similar intensity and affect. Distractor sounds included an ambulance siren, piano, car engine, clock alarm, dogs barking, and the popular song "Do-Re-Me." Each of the 12 sounds (6 test plus 6 distractor) were played for 1 minute in a random fashion as interruptions in soft background music. In this manner an individual's ability to recall and/or recognize a familiar sound heard 24 hours earlier was used as a measure of auditory amnesia in different groups.

Recording of Evoked Potentials

A special purpose data acquisition system, Nicolet, Compact-4 (Nicolet Instruments Inc., Madison, WI), was used in this study to record BAEPs and LLAEPs. All evoked potential recordings were made in duplicate (at each time interval) to document reproducibility and a mean of the two values for latency and amplitude of each component is reported in the numerical data on evoked potentials. Details of recording technique are described below.

Table 1. Stimulation and Recording Parameters for Brain Stem Auditory Evoked Potentials

Site: Right or left ear with [acoustically] shielded earphones
Clicks: Alternating
Rate: 21.1/sec
Intensity: 75 dB above normal hearing level (75 dB nHL)
Duration: 100 microseconds
Masking: None
Electrode placement: Both ear lobes and vertex [CZ*]
Electrode impedence: <3 kΩ
Filters: 150–3000 Hz
Sweep time: 10 milliseconds
Repetitions per average: 2000

*Position designated by the international 10–20 electrode system.

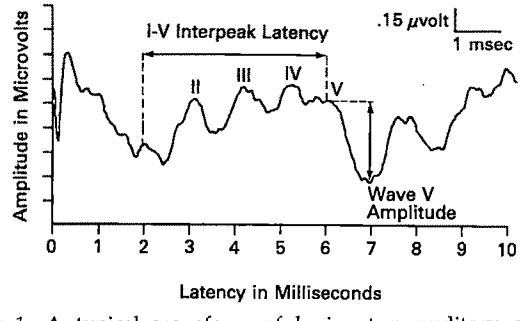

Figure 1. A typical waveform of brain stem auditory evoked potentials in our study. Points for measurement of latency waves of I, V, I–V interpeak latency, and amplitude of wave V have been identified.

BAEPs. Table 1 shows the variables used in our study for recording of BAEPs. A typical waveform of BAEPs thus obtained is shown in Figure 1 with the points for measurements of latency of waves I, V, and interpeak latency I–V, and amplitude of wave V identified. A total of 12 sets of BAEPs were recorded in each subject.

LLAEPs. Recording parameters for LLAEPs are shown in Table 2. Recording of LLAEPs involved the same basic procedure as for BAEPs with the following exceptions. 1) The stimulus train consisted of two computer-generated tones of different pitch presented at slow rates (0.8/sec). 2) The subject was instructed to count and keep a mental record of the number of high-pitched tones that appeared rarely and unpredictably in the train. 3) Computer-stored evoked potentials generated by the two sounds (frequent and rare tones) separately. Figure 2 shows typical LLAEPs thus recorded in one patient. Peak latency and amplitude of N_1 component were measured from the evoked potentials for frequent (1000 Hz) tone. Amplitude of N_1 was taken as the voltage difference between N_1 and P_2 peaks. Latency of P_3 component was obtained from potentials evoked by the rare (2000 Hz) tones, and the amplitude of P_3 was

Table 2. Stimulation and Recording Parameters for Long-Latency Auditory Evoked Potentials

Site: Right or left ear with (acoustically) shielded earphones
Tones: Frequency: 1000 Hz for frequent tones and 2000 Hz for rare tones
Ratio of frequent to rare tones: 80:20
Rate: 0.8/sec
Intensity: 70 dB nHL
Sweep time: 800 milliseconds
Electrode placement: Both ear lobes and vertex (CZ*)
Electrode impendence: <3 kΩ
Filters: 1–30 Hz
Repetitions per recording: 300

*Position designated by the international 10–20 electrode system.

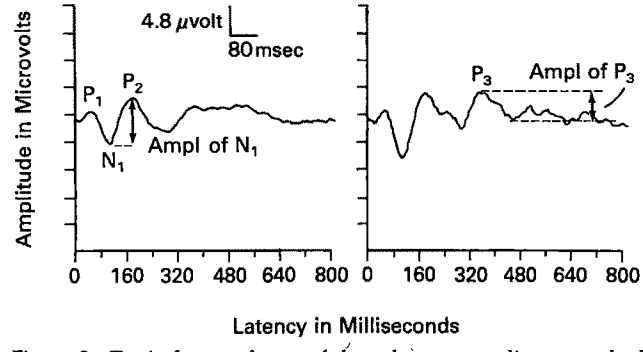

Figure 2. Typical waveform of long-latency auditory evoked potentials. Points for measurement of latency and amplitude of N_1 and P_3 components are identified. Trace on left shows the evoked potentials generated in response to frequent (1000 Hz) tones, whereas those generated by rare (2000 Hz) tones are shown in the trace on right. It should be noted that P_3 appears only in response to those tones that are presented rarely (20%) and unpredictably and is absent in the trace on left.

taken at the most positive point of the peak to the next most negative peak as identified in Figure 2. Twelve (six duplicate) sets of LLAEPs were recorded in each subject.

All waveforms (BAEPs and LLAEPs) were stored on floppy disks for subsequent data analysis. All measurements of latency and amplitude were completed before breaking the code of drugs administered in different groups.

Data for sedation, short-term amnesia, and recall/recognition of test sounds after 24 hours were tabulated. The numerical data for latency and amplitude of various components of auditory evoked potentials were subjected to a 3 (groups) × 6 (trials) mixed-designs analysis of variance for two-factor designs (13). A *P*-value less than 0.05 was considered statistically significant.

Results

Subjects ranged in age from 19 to 40 years with mean age being 28 years in group A and 27 years in groups

Table 3. Short-Term Amnesia in Group C Patients

Time interval after lorazepam (min)	Failure to recollect after*				Total number of errors at all intervals
	Immediately	30 seconds	2 minutes	5 minutes	
0	—	—	—	—	0/18
30	—	a,d,e	a,d,e	a,d,e	9/18
60	—	b	b	b,d,e	5/18
120	—	—	—	c,d,e	3/18
180	—	—	—	—	0/18
240	—	—	e,f	e,f	4/18
Sum of errors in five trials	0/30	4/30	6/30	11/30	

*Six subjects in this group are identified by letters a–f. Dashes indicate the time points when no subject failed to recall. Total number of errors are out of maximum possible of 18 at each interval (six subjects times three chances) in horizontal columns and 30 (six subjects times five trials after drug administration) in vertical columns.

B and C. As expected, blood pressure and heart rate remained stable in all volunteers throughout the study period. Mean change in temperature in all subjects was 0.7°C (range 0.2–1):0.8°C in group A and 0.6°C in groups B and C.

Behavioral Data

Observations pertaining to behavioral data, i.e., grades of sedation, short-term memory, and failure to recall/recognize test sounds 24 hours later, are described below.

Sedation. Placebo produced no sedation. Secobarbital produced mild sedation (range 1.2 to 1.8) up to 4 hours. Lorazepam produced good sedation (range 2.0 to 2.7) up to 4 hours of observation. Subjects in the lorazepam group reported longer duration of sedation when interviewed the next day.

Short-term auditory amnesia. No short-term memory loss was detected either after placebo or secobarbital. Some interesting observations were noted in the lorazepam group as shown in Table 3. Considerable intersubject and intertrial variation was noted. Particularly striking is the lack of short-term antirecall effect at the one hundred-eighty-min interval with higher number of errors noted at 240 minutes. These observations suggest that while short-term amnesia with lorazepam occurs frequently, it is quite inconsistent.

Long-term auditory amnesia. All subjects successfully recalled all test sounds played at time 0. To evaluate the occurrence of long-term amnesia after the administration of drugs, the possible number of erros that could have been made in each group was

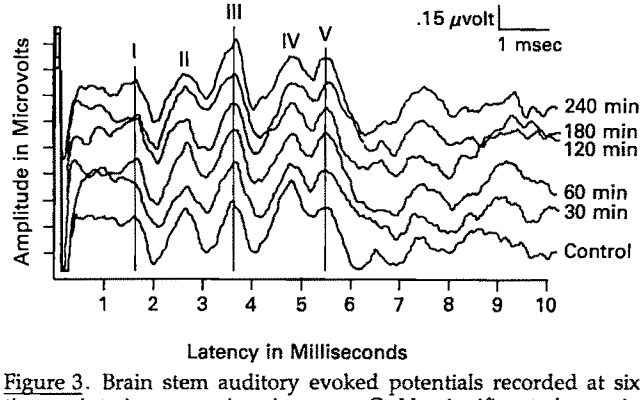

Figure 3. Brain stem auditory evoked potentials recorded at six time points in one patient in group C. No significant change in latency of waves I and V, interpeak latency of I–V, or amplitude of wave V was noted.

calculated by multiplying the number of subjects in each group by number of trials after drug administration (i.e., 5) times 2 (i.e., failure to recall and/or recognize the sounds played). Thus the total number of possible errors was 40 in group A, 50 in group B, and 60 in group C. We observed one error each in groups A and B. Both subjects failed to recall the sound played at 30 minutes but readily recognized it. Twenty-four (out of possible 60) errors were observed in group C. Distribution of these errors at different time intervals is shown in Table 4. Four out of six subjects failed to recall the sounds played 30 and 60 minutes after administration of lorazepam and three of them failed to recognize the sounds. As with short-term amnesia, duration of long-term amnesia varied from subject to subject and did not follow a definite time sequence.

Evoked Potentials Data

Satisfactory recordings of both BAEPs and LLAEPs

Table 4. Long-Term Auditory Amnesia in Group C Patients

Time	Failure to*		Total numbers of errors
	Recall	Recognize	
0	—	—	—
30	a,b,c,d	a,b,d	7/12
60	a,d,e,f	a,d,e	7/12
120	a,c	—	2/12
180	a,b,d	a,b,d	6/12
240	e	e	2/12

*Subjects are identified by same alphabetical letters as in Table 3. Total number of errors are out of maximum possible of 12 at each time interval (six subjects times two chances). Dashes indicate no failure to recall or recognize the test sounds.

were obtained in all subjects. Observations are described in detail later.

BAEPs. Numerical data for BAEPs from all patients is presented in Table 5. There was no significant change in latency of waves 1, V, interpeak latency I–V, or overall morphology as shown in figure 3.

LLAEPs. Changes in latency and amplitude of N_1 and P_3 components in the three groups are diagrammatically shown in Figure 4 and numerical data presented in Table 6. Latency of P_3 remained unchanged in group A and significantly increased ($P < 0.03$) in groups B and C. In group C maximum increase had occurred by 30 minutes and a return toward baseline was noted after 2 hours, although latency was still prolonged at the end of study period (4 hours). The difference between groups B and C was not significant. Amplitude of P_3 decreased compared to control values in all three groups ($P < 0.0001$) and the difference between the groups was not significant. The latency of the N_1 component increased significantly in group C compared to groups A and B ($P < 0.006$). Group A actually showed a slight decrease in N_1 latency at 30 minutes. Maximum change in N_1 latency had occurred by 30 minutes in all groups with a trend to return toward baseline at subsequent intervals. The amplitude of N_1 component also decreased in group C, but not in groups A and B ($P < 0.03$).

Relation between Behavioral Data and LLAEPs

Details of observations regarding short- and long-term amnesia are presented in Tables 3 and 4. Despite the double-blind design of this investigation, subjects in group A were readily identifiable because of lack of sedation. P_3 was well preserved in group A without a noticeable change in latency, but there was marked diminution in amplitude of P_3 with repeated trials as the subject became "bored" with the task. In one subject in group A who failed to recall the test sound played at 30 minutes, P_3 was not any different from other trials or from other subjects in that group. Similarly, in one subject in group B who had no recall at 30 minutes, changes in P_3 latency and amplitude were similar to those at other intervals and in other subjects in the group who did not have any amnesia. Group C patients showed maximum prolongation of latency and decrease in the amplitude of P_3, which was obvious at all the intervals after administration of lorazepam. Changes in P_3 morphology in this group did not bear any definite relation to the failure to recall/recognize the test sounds. For example, subject f had no amnesia except failure to recall at the 1-hour interval, while P_3 was barely recognizable in traces obtained at all intervals after administration of lorazepam. By contrast subject d had no recall or recognition of sounds played at 30, 60, and 180 minutes, while P_3 morphology was well preserved. Therefore, by observing the traces of LLAEPs, we could not predict the time intervals associated with amnesia for test sounds.

Discussion

The aim of this investigation was to study the time course of auditory amnesia after administration of intravenous lorazepam and study the relation, if any, between auditory amnesia and LLAEPs. For the sake of easy comparison we chose to study a dose of lorazepam for which time course of amnesia after visual stimulation has previously been studied (10). To distinguish between the changes in LLAEPs that may result from sedation alone from those that could correlate with amnestic properties of lorazepam, we included another group of subjects who received secobarbital, a short-acting barbiturate that is known to produce sedation for 4 to 6 hours without producing any amnesia (18).

Sedation produced by both seconal and lorazepam in our study was consistent with the doses used. Lack of antirecall effect in groups A and B and amnesia in group C was expected and can be explained on the basis of neuropharmacology of sedatives and anxiolytics. It has been shown in animal studies that barbiturates produce sedation and drowsiness primarily by depression of the reticular activating system, whereas benzodiazepines have a depressant effect on the amygdala and hippocampus (19). The hippocampus has been shown to play a significant

Table 5. Changes in Brain Stem Auditory Evoked Potentials (Mean ± SD)*

Component of evoked potential	Group	Time interval (min) 0	30	60	120	180	240
Wave I latency (milliseconds)	A	1.97 ± 0.6	1.99 ± 0.6	2.02 ± 0.7	2.04 ± 0.7	2.04 ± 0.7	1.99 ± 0.6
	B	1.80 ± 0.2	1.82 ± 0.2	1.85 ± 0.2	1.82 ± 0.2	1.82 ± 0.2	1.88 ± 0.2
	C	1.67 ± 0.1	1.66 ± 0.1	1.67 ± 0.1	1.66 ± 0.1	1.66 ± 0.1	1.67 ± 0.1
Wave V latency (milliseconds)	A	5.92 ± 0.7	5.95 ± 0.7	5.94 ± 0.6	5.94 ± 0.6	5.95 ± 0.6	5.90 ± 0.6
	B	5.88 ± 0.5	5.93 ± 0.4	5.92 ± 0.4	5.89 ± 0.4	5.90 ± 0.4	5.88 ± 0.4
	C	5.56 ± 0.1	5.57 ± 0.1	5.56 ± 0.1	5.55 ± 0.1	5.53 ± 0.1	5.63 ± 0.2
I–V interpeak latency (milliseconds)	A	3.94 ± 0.05	3.95 ± 0.07	3.93 ± 0.09	3.96 ± 0.08	3.91 ± 0.09	3.92 ± 0.03
	B	4.09 ± 0.44	4.11 ± 0.43	4.07 ± 0.38	4.07 ± 0.39	4.09 ± 0.43	4.00 ± 0.35
	C	3.89 ± 0.16	3.91 ± 0.17	3.88 ± 0.18	3.89 ± 0.12	3.88 ± 0.20	3.87 ± 0.19
Amplitude of wave V (μV)	A	0.36 ± 0.12	0.32 ± 0.08	0.31 ± 0.13	0.30 ± 0.12	0.30 ± 0.10	0.34 ± 0.15
	B	0.37 ± 0.14	0.32 ± 0.11	0.31 ± 0.08	0.30 ± 0.08	0.26 ± 0.06	0.27 ± 0.07
	C	0.40 ± 0.11	0.38 ± 0.11	0.43 ± 0.11	0.40 ± 0.11	0.48 ± 0.14	0.44 ± 0.13

*Statistical analysis: No significant difference among the three groups or six trials was detected for any of the components.

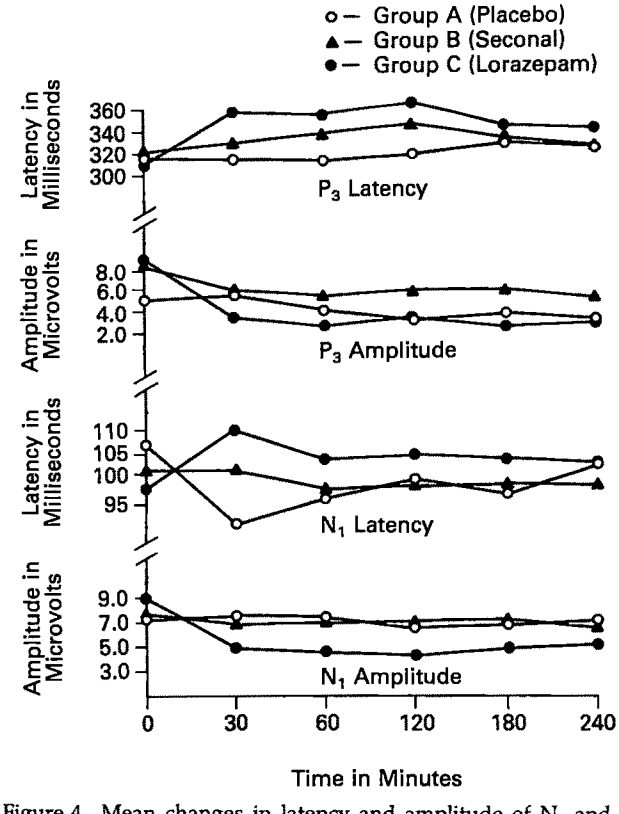

Figure 4. Mean changes in latency and amplitude of N_1 and P_3 components of long-latency auditory evoked potentials in 15 subjects.

role in memory in humans (20,21). No retrograde amnesia was observed because all subjects in group C could correctly recall the sounds played at time 0 after 24 hours. This finding is in keeping with previous reports (10,22,23) of the lack of retrograde amnesia in humans after administration of various premedicant drugs and intravenous and inhalational anesthetics.

Frequency of long-term amnesia with lorazepam in our study was 50–58%, the duration of significant antirecall effect being 3 hours. However, a very small number of errors in recall were observed at 2 hours. Both frequency and duration of amnesia are less in our study compared with those of a previous investigation. Pandit et al. (10) reported 60–80% amnesia for 4 hours after the administration of 4 mg lorazepam. Their study utilized visual stimulation in the form of memory cards. Because no other investigator has utilized auditory stimuli to study the time course of auditory amnesia after lorazepam, a direct comparison is not possible. We have no explanation for the decrease in antirecall effect of lorazepam at the 120-minute interval.

The fact that all subjects could repeat the three-digit number immediately in all trials and number of errors increased at the 30-second, 2-minute, and 5-minute intervals (Table 3) in group C suggests that lorazepam had no effect on reception (registration) of sensory data, and that amnesia was a result of either failure of coding or failure of storage in memory. The fact that most of the subjects who failed to recall the sounds also failed to recognize them further suggests that it is failure to store the information in memory that accounts for lorazepam-induced auditory amnesia. There seems to be no effect on retrieval of stored information as evidenced by lack of retrograde amnesia in group C. This interpretation is based on published information dealing with learning and memory process (20,24).

Lack of significant effect on latency and morphology of various components of BAEPs is in keeping with published literature (25–27) suggesting that latency of various waves of BAEPs, which have their origin in subcortical structures in the brain, are unaffected by a variety of premedicants and narcotic analgesics. Lack of change in I–V interpeak latency of BAEPs, which is a measure of brain stem transmis-

Table 6. Changes in Long-Latency Evoked Potentials (mean ± SD)*

Evoked potential component	Group	Time interval (minutes) 0	30	60	120	180	240
P_3 latency (milliseconds)	A	316 ± 25.6	315 ± 17.9	314 ± 21.1	320 ± 18.1	329 ± 26.1	325 ± 24.9
	B	322 ± 9.6	330 ± 25.4	338 ± 25.8	347 ± 20.8	333 ± 27.7	326 ± 22.7
	C	311 ± 39.3	358 ± 45.9	355 ± 45.7	365 ± 50.4	345 ± 28.9	342 ± 35.7
P_3 amplitude (μV)	A	5.0 ± 1.6	5.4 ± 1.1	4.0 ± 2.2	3.0 ± 0.6	3.7 ± 1.6	3.1 ± 0.7
	B	8.0 ± 4.7	5.8 ± 4.0	5.3 ± 1.2	5.7 ± 2.7	5.8 ± 5.4	5.1 ± 3.9
	C	8.7 ± 4.6	3.4 ± 2.1	2.6 ± 1.0	3.2 ± 2.3	2.5 ± 1.9	2.9 ± 2.2
N_1 latency (milliseconds)	A	107 ± 16.9	94 ± 3.3	96 ± 5.3	100 ± 8.9	97 ± 12.5	103 ± 9.3
	B	102 ± 6.0	102 ± 6.0	98 ± 5.4	99 ± 4.7	99 ± 4.7	99 ± 7.7
	C	98 ± 14.8	110 ± 22.5	104 ± 19.8	105 ± 19.1	104 ± 15.4	103 ± 16.5
N_1 amplitude (μV)	A	7.2 ± 4.1	7.5 ± 3.5	7.3 ± 3.5	6.5 ± 4.4	6.8 ± 3.8	7.1 ± 4.9
	B	7.6 ± 2.5	8.9 ± 1.8	7.0 ± 1.9	6.9 ± 1.3	7.1 ± 1.9	6.5 ± 2.4
	C	8.8 ± 3.4	4.9 ± 1.7	4.6 ± 1.1	4.3 ± 1.2	4.9 ± 0.9	5.3 ± 0.9

*Statistical analysis: P_3 latency: No significant trial effect in group A. Significant trial effect in groups B and C ($P < 0.03$). No significant difference between groups B and C. P_3 amplitude: Significant trial effect in all groups ($P < 0.0001$). No significant difference between groups. N_1 latency: Significant increase in group C ($P < 0.006$). N_1 amplitude: Significant decrease in group C ($P < 0.03$).

sion time and is not affected by stimulation parameters (28) suggests that slowing of transmission through the brain stem did not contribute to the prolongation of latency of N_1 and P_3 components of LLAEPs. The finding of maximum increase in P_3 latency in group C subjects, which also is the group with significant amnesia, gives the erroneous impression that P_3 latency may be a predictor of amnestic effect of lorazepam. It is tempting to draw this conclusion in view of the fact that in humans hippocampal formation has been proposed as a source of P_3 (29), and has been shown to be involved in memory retention (20,21), and P_3 has been suggested to be a physiologic correlate of post-traumatic amnesia after a closed head injury (30). There are several reasons why we feel that increase in latency of P_3 is not a reflection of amnestic properties of lorazepam: 1) The increase in latency of P_3 in groups B and C reflects an effect of generalized sedation rather than being specific for effect on brain structures involved in organization of memory. Had the increase in P_3 latency been specifically related to amnesia we should have seen a significant difference between groups B and C, which we did not see. 2) A significant decrease in amplitude of P_3 suggests that this parameter reflects variability of attention span of the individuals rather than drug effects because there was no significant difference between placebo (group A) and drugs (groups B and C). 3) A concomitant increase in latency and decrease in amplitude of N_1 in group C in both attended and unattended stimuli suggests that changes in LLAEPs are reflection of generalized sedation and not the amnestic properties of lorazepam. The N_1 component has long been known to be influenced by attention (31). Lack of a definite relation between behavioral changes and LLAEPs, i.e., failure to recall the sounds with well-preserved P_3 and increase in P_3 latency and marked diminution of P_3 amplitude at time intervals for which there was no amnesia, further supports the conclusion that changes in P_3 cannot be used as electrophysiologic predictors of amnesia.

Based on the data presented, we conclude that frequency of anterograde auditory amnesia after 0.05 mg/kg lorazepam given intravenously is 50–58%. This effect is observed from 30 minute (earliest interval studied) to 3 hours. Latency and amplitude of P_3 components cannot be used as predictable indicators of auditory amnesia. Lorazepam does not produce retrograde amnesia.

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I-653 Resists Degradation in Rats

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KOBLIN DD, EGER EI, JOHNSON BH, KONOPKA K, WASKELL L. I-653 resists degradation in rats. Anesth Analg 1988;67:534–8.

The ability of rats pretreated with phenobarbital to metabolize a new volatile anesthetic, I-653, was compared with the metabolism of halothane, isoflurane, and methoxyflurane. Each anesthetic was administered for 2 hours at 1.6 MAC (inspired). Control rats were given phenobarbital but not exposed to an anesthetic. In rats pretreated with phenobarbital and exposed to I-653, fluoride ion concentrations in serum and excretion of fluoride ion and organic fluoride in the urine were almost indistinguishable from values measured in control rats. In contrast, rats pretreated with phenobarbital metabolized small but significant amounts of isoflurane. In rats pretreated with ethanol and exposed to I-653, the 24-hour excretion of urinary organic fluoride was nearly ten times greater than that observed in control rats. Marked increases in organic fluoride (as high as 1000 times control values) and/or fluoride ion were found in serum and/or urine after anesthesia of phenobarbital-pretreated rats with halothane or methoxyflurane. The relative stability of I-653 indicates that it may possess minimal toxic properties.

Key Words: ANESTHETICS, VOLATILE—I-653. BIOTRANSFORMATION (DRUGS)-I-653.

I-653 (CF_2H–O–CFH–CF_3) is a new volatile anesthetic that differs from isoflurane (CF_2H–O–CClH–CF_3) by substitution of a fluorine atom for a chlorine atom. This seemingly minor molecular change results in a less soluble compound. The blood/gas and oil/gas partition coefficients for I-653 are 0.42 and 18.7 at 37°C, compared with respective values of 1.4 and 91 for isoflurane (1). This low solubility of I-653 is associated with a rapid recovery from anesthesia. Rats exposed to I-653 awaken from anesthesia three to five times faster than rats exposed to isoflurane at equivalent MAC levels (2). In rats, the MAC of I-653 is 5.7% atm (3).

Because I-653 allows for an exceptionally rapid recovery while permitting a high inspired concentration of oxygen, it may have an advantage over presently used anesthetics. However, before I-653 can be used clinically, it must be shown to be free of toxic effects secondary to metabolic breakdown. In the present study we measured the metabolism of I-653, as assessed by both the appearance of fluoride ion in the serum and the appearance of organic fluoride and fluoride ion in the urine of rats after exposure to I-653. We examined rats pretreated with phenobarbital or ethanol and compared results from those rats with results from non-pretreated rats. Our premise was that enzyme induction would result in maximal breakdown of I-653 in rats.

Materials and Methods

Animals

This study was approved by the UCSF Committee on Animal Research. Specific-pathogen–free male Sprague–Dawley rats, approximately 3 months old and weighing 286–384 g at the start of the experiments, were purchased from Charles River. The rats were housed individually in wire-mesh cages and had continuous access for 1 week to standard rat chow and tap water. Rats were then pretreated either with phenobarbital or ethanol or with a distilled water and rat chow diet.

Enzyme induction with phenobarbital was accomplished by allowing rats continuous access for 5 days to a 1 mg/ml solution in distilled water. Phenobarbital

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was discontinued 24 hours before the anesthetic (I-653, isoflurane, halothane, methoxyflurane) exposures. Control rats were allowed continuous access to the phenobarbital solution for 5 days but were not exposed to an anesthetic.

For I-653, additional studies were performed using non-pretreated and ethanol-pretreated rats. The non-pretreated group was allowed only distilled water for their drinking solution before exposure to I-653. The ethanol-pretreatment group was allowed continuous access for 14 days to a solution containing 16% (v/v) ethanol and 17.3% (w/v) sucrose prepared in distilled water (4). Access continued to the time of exposure to I-653.

After anesthetic exposures, all rats were given distilled water to drink. All rats had continuous access to standard rat chow except during the 2-hour periods of exposure to anesthetics.

Exposure to Volatile Anesthetics

Rats exposed to volatile anesthetics were placed in individual Plexiglas chambers and given an inspired concentration of 1.6 MAC (9.1% I-653, 2.2% isoflurane, 1.7% halothane, or 0.35% methoxyflurane) to breathe for 2 hours. Exposures were carried out between 0700 and 1400 hours. Control rats were treated identically except that they were not placed in the Plexiglas chambers and received no anesthetic. Because of the limited supply of I-653, a previously described (2,5) closed anesthetic system containing dry soda lime was used for all the inhaled agents. After the rats were placed in their individual chambers and exposed to an oxygen flow rate of >1 L/min per rat for 10 minutes, the circuit was sealed and liquid anesthetic was introduced in an amount calculated to produce a rapid rise to 1.6 times MAC. Gas samples were taken from the individual chambers at 5- to 10-minute intervals throughout the 2-hour exposure, and anesthetic concentrations were determined by gas chromatography (3,5). Anesthetic was added as indicated to maintain the concentration of 1.6 MAC. Rectal temperatures were monitored in each rat and maintained between 37.5 and 38.5°C with the use of infrared lamps or by applying ice to the outside of the chambers. Carbon dioxide concentrations in the individual chambers were measured with a Beckman LB-2 infrared analyzer and were typically near 1%, with values ranging between 0.5 and 1.8%.

Collection of Serum and Urine Samples

After the 2-hour anesthetic exposure, rats either were killed immediately by administration of 100% carbon dioxide or were placed into individual metabolic cages. After I-653 and isoflurane exposures, urine samples were collected for periods of 0–4, 4–24, and 24–48 hours. After exposure to halothane or methoxyflurane, and for the control rats, urine collections were obtained over a 24-hour period. At 0, 4, 24, or 48 hours after anesthetic exposure, rats were killed with 100% carbon dioxide. Blood was removed from the inferior vena cava and allowed to clot. The serum was isolated after centrifugation at 1500*g* for 10 minutes. Serum and urine samples were kept frozen at −20 to −30°C before analysis for fluoride.

Fluoride Analyses

Fluoride ion levels in serum and urine were determined using a modified method of Fry and Taves (6). Thawed serum and urine samples were centrifuged at 10,000*g* for 3 minutes to remove particulate material. Twenty microliters of a 5M sodium acetate buffer (pH 4.5) was added to 180 μl of undiluted serum or to 180 μl of a urine sample typically diluted 10-fold. The 200-μl mixture was placed into a machined Teflon cup and fluoride ion concentration was measured using an Orion fluoride ion electrode (model 96-09) with a Corning model 12 pH meter or a Corning 150 ion analyzer. Fluoride ion concentrations in serum or urine were obtained by interpolation of a calibration curve prepared by plotting millivolt values on a linear scale versus the concentration of sodium fluoride standards on a logarithmic scale. Sodium fluoride calibration curves were obtained with the use of distilled water or in the presence of control serum or urine.

The content of nonvolatile organic fluoride in the urine was determined by the sodium fusion method of Soltis and Gandolfi (7). Organic fluoride from urine samples was calculated by subtracting the free fluoride ion in the original sample from the total fluoride content determined by the sodium fusion technique, after correction for the efficiency of organic fluoride detection in rat urine. We found the percentage recovery of fluoride from sodium trifluoroacetate (5 to 60 nmol) dissolved in aqueous solution to be 102 ± 14% (± SD, n = 15). The percentage recovery of fluoride from sodium trifluoroacetate dissolved in control rat urine was 65.5 ± 22.2% (± SD, n = 30). The efficiency of organic fluoride detection in aqueous solution and control rat urine was independent of trifluoroacetate concentration over the range of concentrations examined. Thus, in the calculation of organic fluoride excreted in the urine, we assumed a 65.5% recovery.

Table 1. Serum Concentrations of Fluoride Ion (μM)*

Anesthetic	Pretreatment	Time after anesthetic exposure (hours) 0	4	24	48
None (control)	Phenobarbital	1.0 ± 0.37 (18)			
Isoflurane	Phenobarbital	10.0 ± 3.5†‡ (8)	4.6 ± 1.0†‡ (8)	0.85 ± 0.34 (4)	1.0 ± 0.24 (4)
I-653	Phenobarbital	1.6 ± 0.50§ (8)	1.2 ± 0.15 (8)	1.2 ± 0.10 (4)	1.0 ± 0.08 (4)
I-653	Ethanol	1.0 ± 0.39 (7)	1.1 ± 0.24 (7)	0.74 ± 0.43 (4)	1.5 ± 0.21 (4)
I-653	None	0.56 ± 0.11 (4)	1.3 ± 0.08 (4)	0.80 ± 0.30 (4)	1.1 ± 0.33 (4)
Halothane	Phenobarbital	N.D.	N.D.	1.3 ± 0.15 (5)	N.D.
Methoxyflurane	Phenobarbital	N.D.	N.D.	34.3 ± 6.4‖(5)	N.D.

*Mean values ± SD. The value in parentheses to the right of the mean ± SD indicates the number of measurements, each for a different rat. N.D., not determined. †$P < 0.001$ when compared to phenobarbital-pretreated rats given I-653. ‡$P < 0.001$ when compared to control. §$P < 0.005$ when compared to control. ‖$P < 0.002$ when compared to control.

Table 2. Urinary Excretion of Inorganic Fluoride Ion (nmole/hr)*

Anesthetic	Pretreatment	Time after anesthetic exposure (hours) 0–4	4–24	0–24	24–48
None (control)	Phenobarbital	N.D.	N.D.	88 ± 25 (18)	
Isoflurane	Phenobarbital	325 ± 158† (16)	202 ± 67‡ (8)	220 ± 43†§ (8)	81 ± 34 (4)
I-653	Phenobarbital	81 ± 49 (16)	120 ± 30 (8)	118 ± 27 (8)	66 ± 33 (4)
I-653	Ethanol	85 ± 57 (15)	102 ± 33 (8)	100 ± 33 (8)	108 ± 15 (4)
I-653	None	49 ± 33 (12)	70 ± 16 (8)	68 ± 15 (8)	81 ± 32 (4)
Halothane	Phenobarbital	N.D.	N.D.	187 ± 64‖ (5)	N.D.
Methoxyflurane	Phenobarbital	N.D.	N.D.	1500 ± 212§ (5)	N.D.

*Mean values ± SD. The value in parentheses to the right of the mean ± SD indicates the number of measurements, each for a different rat. N.D., not determined. †$P < 0.001$ when compared to phenobarbital-pretreated rats given I-653. ‡$P < 0.01$ when compared to phenobarbital-pretreated rats given I-653. §$P < 0.001$ when compared to control. ‖$P < 0.05$ when compared to control.

Statistical Analyses

Statistical computations were performed for all groups pretreated with phenobarbital (control, isoflurane, I-653, halothane, and methoxyflurane) at 24 hours after anesthesia with a nonparametric Kruskal–Wallis test using an analog of the Newman–Keuls test for multiple comparisons (8). For these nonparametric analyses, P values of <0.05 were considered statistically significant. The following comparisons were also performed using an unpaired t-test: 1) rats pretreated with phenobarbital and exposed to isoflurane versus those pretreated with phenobarbital and exposed to I-653; 2) control rats (unanesthetized rats treated with phenobarbital) versus rats pretreated with phenobarbital and exposed to isoflurane and; 3) control rats versus those exposed to I-653 and pretreated with phenobarbital or ethanol, or given no pretreatment. For these unpaired t-tests, P values of <0.01 were considered statistically significant.

Results

Fluoride Ion Production after Anesthetic Exposure

Ethanol- or non-pretreated rats given I-653 and phenobarbital-pretreated rats given halothane did not have higher serum fluoride ion concentrations than fluoride ion concentrations compared with unanesthetized control rats (Table 1). A mild elevation in serum fluoride ion was found in phenobarbital-pretreated rats immediately after exposure to I-653. Rats pretreated with phenobarbital and given 1.6 MAC isoflurane for 2 hours had peak serum levels of inorganic fluoride 7- to 10-fold higher than unanesthetized control rats or rats given I-653 for an equivalent number of MAC-hours (Table 1). Serum fluoride ion levels remained elevated for 4 hours after isoflurane exposure but returned to control levels 24 hours after exposure (Table 1). In contrast, serum fluoride ion levels increased markedly after exposure to methoxyflurane (Table 1).

Urinary excretion of fluoride ion was not significantly increased in rats exposed to I-653 (Table 2). Values for urinary excretion of fluoride ion were significantly above control 24 but not 48 hours after anesthesia in rats pretreated with phenobarbital and exposed to isoflurane. For the 24-hour period after anesthetic administration, excretion of fluoride ion in the urine was approximately twice the excretion in unanesthetized control rats after exposure to halothane and 15 times the control value after treatment with methoxyflurane (Table 2).

Table 3. Urinary Excretion of Organic Fluoride (nmole/hr)*

	Pretreatment	Time after anesthetic exposure (hours) 0–4	4–24	0–24	24–48
None (control)	Phenobarbital	N.D.	N.D.	23 ± 21 (18)	
Isoflurane	Phenobarbital	431 ± 166† (16)	243 ± 122‡ (8)	274 ± 108†§ (8)	174 ± 105§ (4)
I-653	Phenobarbital	34 ± 36 (16)	60 ± 40 (8)	54 ± 36 (8)	62 ± 33‖ (4)
I-653	Ethanol	119 ± 135 (13)	213 ± 152 (8)	219 ± 141§ (8)	117 ± 22§ (4)
I-653	None	44 ± 40 (12)	71 ± 34 (8)	68 ± 28§ (8)	65 ± 40§ (4)
Halothane	Phenobarbital	N.D.	N.D.	21,600 ± 7,900§(5)	N.D.
Methoxyflurane	Phenobarbital	N.D.	N.D.	29,300 ± 11,200§ (5)	N.D.

*Mean values ± SD. The value in parentheses to the right of the mean ± SD indicates the number of measurements, each for a different rat. N.D., not determined. †$P < 0.001$ when compared to phenobarbital-pretreated rats given I-653. ‡$P < 0.002$ when compared to phenobarbital-pretreated rats given I-653. §$P < 0.001$ when compared to control. ‖$P < 0.01$ when compared to control.

Nonvolatile Organic Fluoride Production after Anesthetic Exposure

Urinary organic fluoride excretions were elevated 2- to 10-fold above control levels in phenobarbital-pretreated rats exposed to isoflurane or I-653, ethanol-pretreated rats exposed to I-653, or non-pretreated rats exposed to I-653 (Table 3). In contrast, in the 24-hour period after halothane or methoxyflurane administration, the excretion of organic fluoride in the urine was approximately 1000-fold greater than in unanesthetized control rats.

Discussion

The structural similarity of I-653 to the minimally biotransformed anesthetic, isoflurane, the high degree of stability in soda lime (9,10), and the absence of toxic effects in rats exposed to I-653 (5,11) are consistent with our finding that I-653 undergoes minimal biotransformation in the intact animal. When compared to results from unanesthetized control animals, fluoride ion concentrations in serum and excretion of fluoride ion in urine exhibited little or no increase after administration of I-653 to phenobarbital-pretreated, ethanol-pretreated, or non-pretreated rats. In contrast, peak fluoride ion concentrations in serum after isoflurane administration to phenobarbital-pretreated rats reached values approximately one order of magnitude higher than control levels. Halothane and methoxyflurane underwent marked biodegradation as indicated by dramatic increases in serum fluoride ion concentration or urinary fluoride excretion.

Because no previous information was available concerning the possible metabolic breakdown of I-653, we measured fluoride levels in both non-pretreated and pretreated rats. We employed phenobarbital and ethanol as inducers of microsomal enzymes because each of these drugs increase specific forms of cytochrome P-450. Rats treated with phenobarbital have a 39-fold increase in cytochrome P-450b and a 2-fold increase in cytochrome P-450a in hepatic microsomes (12). Rats given ethanol produce a unique liver isozyme called cytochrome P-450j (13).

Long-term administration of alcohol increases the microsomal metabolism of several inhaled anesthetics (4,14). However, anesthetic metabolism may occur only at very specific times after termination of long-term ethanol treatment and may depend on the level of ethanol present when the anesthetic is administered. For example, enflurane defluorination in vivo was almost completely inhibited immediately after chronic treatment, increased to 9.3 times the control level 4 hours after chronic treatment was stopped, and decreased to control level 12 hours after removal of ethanol (15). In the present experiments, rats were exposed to I-653 immediately after chronic treatment with ethanol. Although no significant elevation in serum fluoride levels or urinary excretion of fluoride ion was detected (Tables 1 and 2), excretion of organic fluoride in the urine for the 24 hours after I-653 exposure was approximately ten times the control value (Table 3).

The sodium fusion assay used to determine organic fluoride excreted in the urine (Table 3) has limitations (16). Volatile metabolites produced by metabolic breakdown of the inhaled anesthetics would not be detected with this assay (16). Furthermore, sodium trifluoroacetate was used as a model compound for the calculation of the percentage recovery of fluoride. Other metabolic byproducts may give a different efficiency of organic fluoride detection. Using sodium trifluoroacetate, we found the percentage recovery of fluoride in rat urine to be 65.5%, a value between the previously reported values of 48% (7) and 83% (16).

In summary, compared to values for unanesthetized control rats, serum fluoride ion concentration and the amounts of organic fluoride or fluoride ion

excreted in the urine exhibit little or no increase in phenobarbital-pretreated or non-pretreated rats exposed to I-653. A mild elevation in urinary excretion of organic fluoride was detected in ethanol-pretreated rats exposed to I-653. These results suggest that I-653 undergoes minimal biodegradation. The possibility that I-653 undergoes metabolism to compounds that covalently bind to tissues and thus would not appear in the blood or urine remains to be examined.

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Myocardial Blood Flow and Oxygen Consumption during Isovolemic Hemodilution Alone and in Combination with Adenosine-Induced Controlled Hypotension

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CRYSTAL GJ, ROONEY MW, SALEM MR. Myocardial blood flow and oxygen consumption during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. Anesth Analg 1988;67:539–47.

Recent reports have proposed combining isovolemic hemodilution and controlled hypotension to limit blood loss during surgery. Before such a technique can be considered for clinical use, it must be demonstrated that it does not endanger maintenance of adequate myocardial oxygenation. Accordingly, measurements of left ventricular myocardial blood flow and oxygen consumption were obtained during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension in ten pentobarbital-anesthetized, open chest dogs with normal coronary circulation. Hemodilution to a hematocrit of 21.7% was produced by isovolemic exchange of whole blood for 5% dextran. In the presence of hemodilution, adenosine was infused intravenously at a rate sufficient to decrease mean aortic pressure to 51 mm Hg. Myocardial blood flow was measured with radioactive microspheres and used to calculate global left ventricular myocardial oxygen consumption and oxygen supply. Hemodilution alone increased aortic blood flow (+43%) but had no effect on aortic pressure, left atrial pressure, heart rate, or left ventricular dP/dt_{max}; an increase in myocardial blood flow (+130%) maintained oxygen supply and consumption at the baseline level. Adenosine-induced hypotension during hemodilution decreased heart rate (−35%), left ventricular dP/dt max (−28%), and aortic blood flow (−14%). These systemic responses were accompanied by reduced myocardial oxygen consumption (−29%) and increased myocardial blood flow (+54%) and myocardial oxygen supply (+72%). These latter effects resulted in reduction in the coronary arteriovenous oxygen content difference and in an attendant rise in coronary sinus P_{O_2} (+66%), which are signs of luxuriant myocardial perfusion. The present study demonstrated in anesthetized dogs that 1) myocardial oxygenation is well maintained during isovolemic hemodilution alone and, 2) myocardial oxygenation is influenced favorably when isovolemic hemodilution is combined with adenosine-induced controlled hypotension. Further studies are required to evaluate the safety of the latter condition in hearts with stenotic coronary arteries.

Key Words: ANESTHETIC TECHNIQUES—hypotensive. HEART—myocardial oxygenation. BLOOD—hemodilution.

Adenosine, a metabolic breakdown product of adenosine triphosphate, is an endogenous vasodilator that has been implicated in local regulation of coronary blood flow (1). The drawbacks of currently used hypotensive drugs, halothane, nitroglycerin, nitroprusside, and trimethaphan, which include cyanide toxicity, tachyphylaxis, reflex tachycardia, rebound hypertension, and excessive cerebral vasodilation (2–5), have stimulated interest in the use of exogenous adenosine to induce controlled hypotension (2,7–9).

Intravenous infusion of adenosine causes arterial hypotension that is rapidly achieved, easily controlled, short-lived and, furthermore, is not associated with any apparent hematologic or biochemical evidence of toxicity (2,7,8). An additional advantage of adenosine-induced hypotension is its beneficial effect on myocardial oxygen supply/demand balance, because it increases coronary blood flow (myocardial oxygen supply) while at the same time decreasing myocardial oxygen demand (9).

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Recent reports (10,11) have described the usefulness of combining controlled hypotension with isovolemic hemodilution, another method of blood conservation. Because the coexistence of depressed driving pressure for coronary blood flow and reduction in oxygen carrying capacity of the arterial blood may risk development of myocardial hypoxia, studies of myocardial oxygen supply/demand relations are necessary before a technique of combined hemodilution and hypotension can be considered for clinical application. Such studies would have additional clinical relevance insofar as they relate to the widespread use of large volumes of intravenous balanced electrolyte solution for management of hypotension during spinal anesthesia (12).

The present study was performed to assess the effect of isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension on myocardial blood flow and oxygen consumption in normal hearts of anesthetized dogs.

Methods

Experimental Preparation

Experiments were performed on ten mongrel, heartworm-free, conditioned dogs of either sex (weight range 21–24 kg), anesthetized with pentobarbital sodium, 30 mg/kg IV initially, with supplementation as required to maintain a stable anesthetic state. The rate of supplementation was approximately 2 $mg \cdot kg^{-1} \cdot hr^{-1}$. After tracheal intubation, the dogs were ventilated by a Harvard respiratory pump with room air. Physiologic values for arterial Po_2, Pco_2, and pH were established initially by adjusting the volume and rate of the respirator and adding oxygen to the inspired gas, and by administering sodium bicarbonate solution to correct mild anesthesia-induced metabolic acidosis. These values remained unchanged during the course of the experiment. Blood gas analysis was performed electrometrically (Radiometer, model ABL-1, Copenhagen, Denmark). Rectal temperature was monitored and maintained at 38°C with a heating pad.

Polyethylene cannulas were inserted into 1) the thoracic aorta via the right femoral and right brachial arteries for monitoring aortic blood pressure and for obtaining samples of arterial blood for analysis of gas tensions and, 2) the right femoral vein for administration of supplementary anesthetic and other intravenous injections. The heart was exposed through a left thoracotomy in the fourth intercostal space. Polyethylene cannulas were inserted into 1) the left atrium via the atrial appendage for monitoring left atrial pressure and for injecting radioactive microspheres, 2) the left ventricle via the left atrial appendage and the mitral valve for measuring left ventricular pressure and, 3) the left femoral vein and right carotid artery for isovolemic exchange of whole blood with dextran solution. A noncannulating flow transducer was placed around the ascending aorta to measure cardiac output (less coronary blood flow) using an electromagnetic flowmeter (Narco Biosystems). Heparin 300 U/kg IV was administered to prevent blood coagulation in exchange circuits.

Vascular pressures were measured with Statham transducers (model P23ID) and averaged electronically. The left ventricular systolic pressure pulse was used to drive a cardiotachometer and it was differentiated electronically to yield dP/dt max (13). Blood pressures, aortic blood flow, and heart rate were recorded with a Gould recorder (model 2800S). Systemic vascular resistance (excluding coronary bed) was computed by dividing mean aortic pressure by mean aortic blood flow.

The statistical significance of differences between treatment means was tested using a randomized block analysis of variance in conjunction with the Student–Newman–Keuls test (14). $P < 0.05$ was considered statistically significant throughout this study.

Measurement of Regional Myocardial Blood Flow

Regional myocardial blood flow was measured with 15 ± 3 μm microspheres labeled with γ-emitting radionuclides, ^{141}Ce, ^{51}Cr, ^{46}Sc, ^{85}Sr, and ^{113}Sn (New England Nuclear Corp.; 3M Co.). After the microspheres enter the coronary circulation, their distribution follows that of myocardial perfusion (15) and they undergo complete entrapment under control conditions as well as during hemodilution (16). Before injection, microspheres were dispersed in a solution of 10% dextran and agitated in a vortex mixer and in an ultrasonic bath. Approximately 1×10^6 microspheres were administered for each flow determination. The microspheres were flushed into the left atrium over 30 seconds with 5 ml body temperature isotonic saline. Administration of microspheres had no detectable effect on monitored hemodynamic variables. Beginning simultaneously with each microsphere injection, duplicate reference arterial samples were collected for 3 minutes through two cannulas of different lengths inserted into the aorta via the left femoral artery. Similar radioactivities of these duplicate reference samples verified adequate mixing of microspheres in the left ventricular output.

After the final injection of microspheres, the heart was stopped by intravenous injection of KCl, excised,

and frozen to facilitate transmural sampling. Full-thickness myocardial samples were obtained from the left ventricular free wall, the right ventricular free wall, and the interventricular septum. The left ventricular and septal samples were cut into thirds transmurally and the right ventricular samples were cut into halves transmurally to yield regional sections weighing at least 1.0 g each. Each section was transferred to a tared counting tube. The tissue and reference blood samples were weighed and analyzed for radioactivity with a scintillation counter equipped with a multichannel analyzer (LKB model 1282-002). Isotope separation was accomplished by standard techniques of γ spectroscopy. Values for regional myocardial blood flow (rMBF) (in $ml \cdot min^{-1} \cdot 100\ g^{-1}$) were calculated from the equation:

$$rMBF = ABF \times (MC/AC) \times 100,$$

where ABF is the arterial reference sampling (ml/min), MC is microsphere radioactivity ($counts \cdot min^{-1} \cdot g^{-1}$) in the myocardial samples, and AC is the total microsphere radioactivity (counts/min) in the arterial reference samples. All myocardial samples contained more than 400 microspheres, which was sufficient to ensure high-precision, low-error flow measurements (17). Values for rMBF within each left and right ventricular free wall and interventricular septum were averaged to compute a value for mean transmural blood flow.

Measurement of Global Myocardial Oxygen Consumption

In seven of the dogs a cannula was introduced into the coronary sinus via the right jugular vein and right atrium for collecting samples of venous effluent from the left ventricular myocardium. Blood samples were simultaneously collected anaerobically from the aorta and the coronary sinus to determine the left coronary arteriovenous oxygen content difference. Oxygen content of blood samples was measured with a Lex-O_2-Con (Lexington Instruments).

Global myocardial oxygen consumption of the left ventricular free wall (MVo_2) (in $ml \cdot min^{-1} \cdot 100\ g^{-1}$) was calculated from the Fick equation:

$$MVo_2 = MBF \times [(a-v)O_2 \text{ difference}/100],$$

where MBF is mean transmural left ventricular myocardial blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$) and $(a-v)O_2$ difference is the left coronary arteriovenous oxygen content difference (vol%). Values for myocardial oxygen supply were computed by multiplying myocardial blood flow and arterial oxygen content.

Experimental Protocols.

Dogs were permitted to stabilize physiologically for at least 30 minutes after surgical preparation before baseline measurements of myocardial blood flow, oxygen supply, and oxygen consumption were obtained. Isovolemic hemodilution was produced by removing blood from a carotid artery at a rate of 20 ml/min while replacing it with 5% dextran (molecular weight 40,000; American McGaw) pumped into the left femoral vein at the same rate. The total volume exchanged was 45 ml/kg. A second set of myocardial measurements was obtained after the preparation was permitted to stabilize for 15 minutes after completion of fluid exchange. Adenosine (60 mmol/L in isotonic saline) was then infused intravenously at a rate of 81–300 μmol/min (mean 184 $\pm$ 31), a rate sufficient to reduce mean aortic blood pressure by 50%. The rate of infusion of adenosine was held constant throughout the hypotensive period. Because a highly concentrated adenosine solution was used, low infusion rates (3.1 $\pm$ 0.5 ml/min) prevented further decreases in arterial hematocrit during controlled hypotension. The adenosine solution required continual heating and stirring to avoid precipitation of adenosine crystals. In all dogs measurements were obtained 15 minutes after the start of adenosine infusion. In four of the dogs, measurements were also obtained 60 minutes after the start of adenosine infusion and after stoppage of adenosine infusion and partial restoration of hematocrit by isovolemic return of the previously withdrawn blood. Replacement of blood samples obtained for analysis of gas tensions and radioactivity levels was performed with autologous blood throughout all experiments to maintain isovolemic conditions.

Results

Systemic Effects (Table 1)

Hemodilution caused a 52% reduction in arterial hematocrit and a proportional reduction in arterial oxygen content. An increase in aortic blood flow (+43%) blunted the decrease in systemic oxygen supply caused by this reduction in arterial oxygen content. Hemodilution reduced systemic vascular resistance (−37%), while it had no significant effect on aortic blood pressure, left atrial pressure, left ventricular dP/dt max, or heart rate.

Data during hemodilution alone served as a reference for evaluating effects of intravenous infusion of adenosine. Adenosine infusion, at a rate sufficient to decrease mean aortic pressure by one-half, reduced

Table 1. Changes in Systemic Hemodynamic Variables during Hemodilution Alone and during Combined Hemodilution and Adenosine-Induced Controlled Hypotension*

	Control	Hemodilution alone	Hypotension during hemodilution
Mean aortic pressure (mm Hg)	110 ± 6	103 ± 5	51 ± 3†,‡
Systolic aortic pressure (mm Hg)	125 ± 6	124 ± 4	77 ± 3†,‡
Diastolic aortic pressure (mm Hg)	101 ± 6	92 ± 5	42 ± 3†,‡
Mean left atrial pressure (mm Hg)	4.3 ± 0.5	6.1 ± 0.7	5.7 ± 1.0
Left ventricular dP/dt max (mm Hg/sec)	1700 ± 93	1815 ± 137	1315 ± 137†,‡
Heart rate (beats/min)	163 ± 11	160 ± 9	104 ± 4†,‡
Aortic blood flow (ml/min)	1182 ± 135	1691 ± 187†	1453 ± 175†,‡
Systemic vascular resistance (excluding coronary bed) (mm Hg·ml^{-1}·min^{-1})	0.106 ± 0.014	0.067 ± 0.007†	0.041 ± 0.007†,‡
Arterial hematocrit (%)	44.9 ± 2.4	21.7 ± 1.6†	22.0 ± 1.9†
Arterial oxygen content (vol%)	21.2 ± 1.2	9.6 ± 0.8†	10.0 ± 1.0†
Systemic oxygen supply (ml/min)	251.7 ± 34.5	163.5 ± 26.6†	131.6 ± 17.1†

*Values are mean SE in ten dogs.
†$P < 0.05$, from control.
‡$P < 0.05$, from hemodilution alone.

Table 2. Changes in Mean Transmural and Regional Myocardial Blood Flow (in ml·min^{-1}·100 g^{-1}) during Hemodilution Alone and during Combined Hemodilution and Adenosine-Induced Controlled Hypotension*

	Control	Hemodilution alone	Hypotension during hemodilution
Left ventricular free wall			
Mean transmural	61 ± 4	140 ± 12†	230 ± 27†,‡
Subepicardium	60 ± 4	132 ± 15†	269 ± 29†,‡
Midmural	59 ± 4	138 ± 17†	225 ± 30†,‡
Subendocardium	64 ± 5	148 ± 18†	177 ± 24†
Endo:epi ratio	1.05 ± 0.05	1.12 ± 0.06	0.67 ± 0.05†,‡
Right ventricular free wall			
Mean transmural	40 ± 4	82 ± 6†	251 ± 20†,‡
Subepicardium	41 ± 5	80 ± 7†	246 ± 20†,‡
Subendocardium	39 ± 4	85 ± 6†	255 ± 25†,‡
Endo:epi ratio	1.00 ± 0.07	1.10 ± 0.09	1.03 ± 0.03
Interventricular septum			
Mean transmural	62 ± 4	141 ± 13†	212 ± 21†,‡
Right ventricle	53 ± 4	117 ± 10†	232 ± 26†,‡
Midmural	65 ± 6	148 ± 15†	243 ± 23†,‡
Left ventricle	67 ± 6	156 ± 16†	191 ± 22†
RV:LV ratio	1.33 ± 0.11	1.35 ± 0.08	0.83 ± 0.05†,‡

*Values are mean ± SE in ten dogs.
†$P < 0.05$, from control.
‡$P < 0.05$, from hemodilution alone.

left ventricular dP/dt max (−28%), heart rate (−35%), aortic blood flow (−14%), and systemic vascular resistance (−39%). Other systemic vascular variables were unchanged.

Myocardial Effects

Hemodilution caused increases in transmural myocardial blood flow (Table 2) that were sufficient to maintain oxygen supply at the baseline level (Table 3). There was no transmural heterogeneity in myocardial vascular responses during hemodilution.

Adenosine infusion increased mean transmural blood flow in the left (+64%) and right (+206%) ventricular free walls, as well as in the interventricular septum (+152%), with resultant proportional increases in local oxygen supply.

Within the left ventricular free wall, the adenosine-induced increase in blood flow (and also in oxygen

Table 3. Changes in Mean Transmural and Regional Myocardial Oxygen Supply (in $ml \cdot min^{-1} \cdot 100\ g^{-1}$) during Hemodilution Alone and during Combined Hemodilution and Adenosine-Induced Controlled Hypotension*

	Control	Hemodilution alone	Hypotension during hemodilution
Left ventricular free wall			
Mean transmural	12.8 ± 1.1	12.8 ± 1.4	22.0 ± 3.4†,‡
Subepicardium	12.6 ± 1.0	12.2 ± 1.2	26.1 ± 3.8†,‡
Midmural	12.5 ± 1.2	12.8 ± 1.5	22.2 ± 3.8†,‡
Subendocardium	13.4 ± 1.2	13.8 ± 1.6	17.6 ± 2.8
Right ventricular free wall			
Mean transmural	8.7 ± 1.2	7.7 ± 0.7	25.4 ± 3.5†
Subepicardium	8.8 ± 1.2	7.5 ± 0.7	24.8 ± 3.3†,‡
Subendocardium	8.6 ± 1.1	7.9 ± 0.7	25.9 ± 3.8†,‡
Interventricular septum			
Mean transmural	13.0 ± 0.9	13.2 ± 1.3	22.4 ± 3.3†,‡
Right ventricle	11.1 ± 1.0	10.9 ± 1.0	23.6 ± 3.7†,‡
Midmural	13.9 ± 1.2	14.1 ± 1.6	24.6 ± 3.5†,‡
Left ventricle	14.1 ± 1.0	14.5 ± 1.6	18.9 ± 2.8

*Values are mean ± SE in ten dogs.
†$P < 0.05$, from control.
‡$P < 0.05$, from hemodilution alone.

Table 4. Changes in Global Left Ventricular Myocardial Oxygen Consumption and Related Variables during Hemodilution Alone and during Combined Hemodilution and Adenosine-Induced Controlled Hypotension*

	Control	Hemodilution alone	Hypotension during hemodilution
Myocardial oxygen consumption ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	8.4 ± 0.8	9.2 ± 0.9	6.0 ± 1.1†,‡
Mean myocardial blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	62 ± 6	145 ± 23†	224 ± 31†,‡
Coronary (a-v)O_2 difference (vol%)	13.9 ± 1.4	6.9 ± 0.7†	2.7 ± 0.4†,‡
Coronary sinus PO_2 (mm Hg)	32.6 ± 1.8	33.1 ± 1.8	55.1 ± 2.3†,‡

*Values are mean ± SE in seven dogs.
†$P < 0.05$, from control.
‡$P < 0.05$, from hemodilution alone.

supply) was evident in the subepicardium and midmyocardium, but not in the subendocardium. This reduced the endo:epi flow ratio by 40%. The pattern of flow response in the interventricular septum during adenosine infusion was similar to that in the left ventricular free wall. Within the right ventricular free wall, the adenosine-induced increase in flow, as well as in oxygen supply, was transmurally uniform.

Table 4 presents values for global left ventricular myocardial oxygen consumption and related variables. Hemodilution alone caused no significant change in myocardial oxygen consumption because the increases in blood flow were sufficient to offset the reductions in coronary arteriovenous oxygen content difference. Coronary sinus Po_2 was stable. Adenosine infusion during hemodilution reduced myocardial oxygen consumption (−35%), while it raised myocardial blood flow (+54%). This resulted in decreases in coronary arteriovenous oxygen content difference (−61%) and resultant increases in coronary sinus Po_2 (+66%).

Figure 1 shows that 1) when adenosine infusion was extended to 60 minutes, the effects noted earlier for 15 minutes of adenosine infusion persisted and, 2) that these effects were readily reversed after stoppage of adenosine infusion and return of hematocrit toward baseline.

Discussion

Effects of Hemodilution Alone

The tendency for increases in myocardial blood to maintain local oxygen supply during isovolemic hemodilution has been demonstrated previously (18,19). Because aortic pressure (coronary driving pressure) did not vary, these increases in myocardial blood flow resulted from decreased vascular resis-

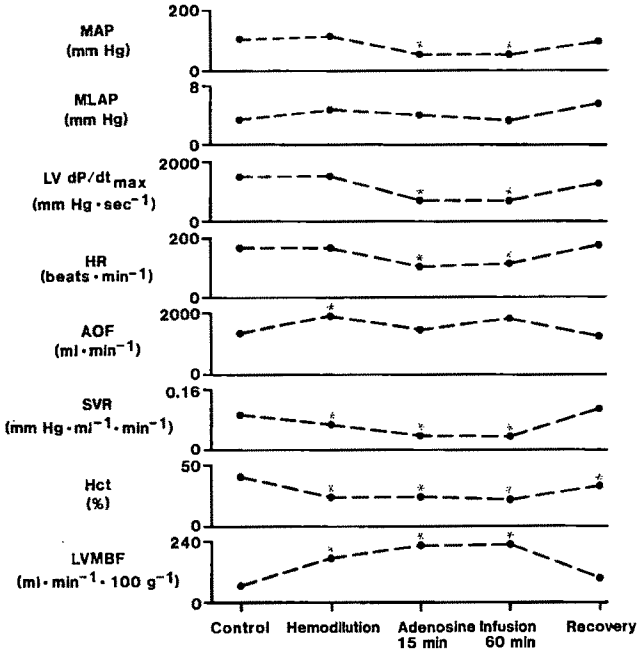

Figure 1. Mean values for cardiovascular variables during isovolemic hemodilution alone and combined with adenosine-induced controlled hypotension (15 and 60 minutes) and after recovery in four dogs. Abbreviations: MAP, mean aortic pressure; MLAP, mean left atrial pressure; LV dP/dt max, left ventricular dP/dt max; HR, heart rate; AOF, aortic blood flow; SVR, systemic vascular resistance; Hct, hematocrit; LVMBF, left ventricular myocardial blood flow. *$P < 0.05$, from control.

tance secondary to the combined effects of reduced blood viscosity and autoregulatory coronary vasodilation (16,18).

The transmurally uniform increases in left ventricular myocardial blood flow during hemodilution in the present study contrast with the relative subendocardial hypoperfusion demonstrated previously (20,21). A possible explanation for this apparent discrepancy is the tachycardia and aortic hypotension that occurred in these previous studies, factors that have been demonstrated to reduce the endocardium/epicardium flow ratio in dilated left coronary circulations (22). This explanation is supported by our recent report (16) that, with hemodynamic variables controlled, selective hemodilution in the left anterior descending coronary artery caused equivalent increases in subendocardial and subepicardial blood flow.

The finding that myocardial oxygen consumption of the left ventricle remained at control levels during hemodilution alone does not necessarily indicate that the prevailing myocardial oxygen demand was satisfied. A factor tending to increase myocardial oxygen demand under this condition was elevated cardiac output (23), which tended to preserve systemic oxygen delivery in the presence of reduced arterial oxygen content. However, this factor should have been counterbalanced at least in part by reduction in left ventricular afterload, because of decreased impedance to left ventricular ejection due to reduced blood viscosity and peripheral vasodilation (24). Several lines of evidence suggest that oxygen demands of the left ventricular myocardium are satisfied during hemodilution. First, oxygen tension of coronary sinus blood remained at the baseline level (Table 4). This suggests that mean tissue oxygen tension, a reflection of tissue oxygen supply/demand balance (25), was preserved. Second, monitored indexes of global cardiac performance, e.g., left atrial pressure, and left ventricular dP/dt, were stable (Table 1). Third, previous studies demonstrated no ischemic changes in local electrograms (21) and continued uptake of lactate suggesting lack of anaerobic metabolism (26).

Constraints of venous sampling precluded measurements of myocardial oxygen consumption in the right ventricular wall, septum, and within regions of the left ventricular wall. However, because flow increases during hemodilution were adequate to maintain basal levels of oxygen supply in these areas of the heart, there is no reason to suspect localized deficits in myocardial oxygenation.

Effects of Combined Isovolemic Hemodilution and Adenosine-Induced Hypotension

Adenosine-induced hypotension during isovolemic hemodilution was caused primarily by a decrease in systemic vascular resistance, although cardiac output decreased marginally because of bradycardia. This bradycardia was apparently due to direct suppression of pacemaker activity in the sinoatrial node by adenosine (27) that was adequate to override the baroreflex-mediated increase in heart rate associated with aortic hypotension itself (10).

Combined isovolemic hemodilution and adenosine-induced controlled hypotension favorably influenced global left ventricular myocardial oxygen supply/demand balance, because it increased oxygen supply while at the same time reducing oxygen demand. This resulted in reduction in myocardial oxygen extraction and an attendant increase in coronary sinus oxygen tension, which are signs of luxuriant myocardial perfusion (22).

Adenosine raises coronary blood flow by causing direct relaxation of arteriolar vascular smooth muscle (28). The appreciable increases in myocardial perfusion that adenosine caused in the present study occurred in the presence of 50% reduction in driving pressure and after a portion of the flow reserve had

been presumably recruited to preserve myocardial oxygenation during hemodilution alone, which is evidence for an extensive vasodilator reserve capacity in the coronary circulation. Another mechanism contributing to elevated left ventricular myocardial blood flow during adenosine infusion was attenuation of the systolic extravascular component of coronary vascular resistance because of bradycardia and reduced intramyocardial pressure secondary to reduced left ventricular intracavitary pressure (22).

In the left ventricular free wall, the increase in myocardial blood flow during adenosine infusion in the presence of hemodilution was confined to the superficial layers, which meant that the endocardium/epicardium flow ratio decreased. Such relative subendocardial hypoperfusion, also observed during coronary insufficiency (16), likely reflects a greater intravascular pressure requirement in the subendocardium to reopen vessels compressed by high systolic intramyocardial pressures (29). Although, as stated earlier, adenosine probably attenuated extravascular compression in the left ventricular free wall, this factor apparently remained sufficient to restrict subendocardial flow. The finding that flow was less in the subendocardium should not be interpreted as evidence that ischemia occurred selectively in that region. Inasmuch as oxygen supply in the subendocardium remained at the preadenosine level while local oxygen demands were presumably depressed, oxygen supply was likely excessive there as it was across the left ventricular free wall.

In contrast to findings in the left ventricular free wall, adenosine caused transmurally uniform increases in flow in the right ventricular free wall. This observation is consistent with the lack of significant extravascular compression of subendocardial vessels in the right ventricular free wall because of lower intracavitary and myocardial tissue pressures during systole (30). The transmural pattern of flow increase in the interventricular septum during adenosine infusion reflected the difference in subendocardial flow response observed for the left and right ventricular free walls.

The reduction in myocardial oxygen consumption of the left ventricular free wall during adenosine infusion is likely to be the main result of the decreases in heart rate and left ventricular pressure (in accordance with the law of Laplace a reflection of wall tension) (23). It is also unclear whether a reduction in myocardial contractility, the third primary determinant of myocardial oxygen demand, was also involved. Although in vitro studies suggest that adenosine may inhibit transsarcolemmal movement of calcium (31), we previously observed no change in local myocardial oxygen consumption and segment shortening during intracoronary infusion of adenosine in in situ canine hearts (28,32). Furthermore, although adenosine infusion in the present study was associated with considerable decreases in left ventricular dP/dt max, concomitant reductions in aortic pressure and heart rate rendered this measurement an unreliable index of global left ventricular myocardial contractility (33).

Among the other drugs currently used to induce clinical hypotension, only trimethaphan, a drug free of significant direct coronary vasodilator effects (10), has been studied in the myocardium in the presence of hemodilution (34). In contrast to the present findings, combined isovolemic hemodilution and trimethaphan-induced hypotension caused no change in the rate of coronary blood flow and reduced myocardial oxygen supply by 55%. On the basis of a proportional reduction in "pressure-rate" product, the authors concluded that myocardial oxygen supply vs demand balance was nevertheless preserved, although this was not verified by analysis of coronary venous blood samples or of other indexes of myocardial ischemia, e.g., ECG.

The persistence of coronary and systemic hemodynamic responses during the 60-minute infusion of adenosine is in keeping with previous studies (2,32) demonstrating that the circulation does not develop tachyphylaxis to effects of adenosine.

Because the present findings were obtained in normal, healthy dogs with unobstructed coronary arteries, the effect of combined isovolemic hemodilution and adenosine-induced hypotension in the heart with coronary artery disease, a condition found frequently in human patients, can only be speculated on. However, two factors suggest that a decrease in blood flow through the stenotic coronary artery might be expected. First, reduced vasodilator reserve capacity because of proximal coronary obstruction makes blood flow more pressure dependent and thus vulnerable to decrease when aortic pressure is reduced. Second, adenosine-induced dilation of resistance vessels in the normal myocardium would likely divert flow away from the flow-restricted bed, the so-called "coronary steal phenomenon" (35). Although reduced blood viscosity due to hemodilution may compensate for decreases in coronary blood flow due to these factors, it does so, of course, at the cost of reduced oxygen-carrying capacity of the arterial blood and myocardial oxygen supply remains below normal (16). Despite the anticipated decrease in oxygen supply in the stenotic coronary bed during combined isovolemic hemodilution and adenosine-induced hypotension, simultaneous reductions in

myocardial oxygen demands (see earlier) make it impossible to predict whether myocardial ischemia will follow.

Although not exactly analogous to the condition of combined hemodilution and hypotension evaluated in the present study, a recent clinical study (12) may provide insight into myocardial effects of this condition in ischemic hearts. In this study, left ventricular function was assessed with radionuclide angiography while volume loading with lactated Ringer's solution was performed to correct aortic hypotension induced by epicardial anesthesia in patients with a history of angina pectoris. The results demonstrated that although anesthesia-induced hypotension itself caused modest improvements in ventricular function (presumably because of reduced afterload), this benefit was negated by subsequent infusion of cell-free crystalloid solution. Although it is tempting to attribute the reemergence of myocardial dysfunction to hemodilution itself, the tendency for hypervolemia to increase global cardiac work requirements cannot be ruled out.

In conclusion, the present findings obtained in normal canine hearts demonstrate that myocardial oxygenation is maintained during isovolemic hemodilution alone and that it is influenced favorably when such hemodilution is combined with adenosine-induced controlled hypotension. Further studies are required to evaluate the safety of the latter method of blood conservation in the heart with stenotic coronary arteries.

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Fentanyl–Diazepam Anesthesia with or without N_2O Does Not Attenuate Cardiopulmonary Baroreflex-Mediated Vasoconstrictor Responses to Controlled Hypovolemia in Humans

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EBERT TJ, KOTRLY KJ, MADSEN KE, BERNSTEIN JS, KAMPINE, JP. Fentanyl–diazepam anesthesia with or without N_2O does not attenuate cardiopulmonary baroreflex-mediated vasoconstrictor responses to controlled hypovolemia in humans. Anesth Analg 1988;67:548–54.

Cardiopulmonary baroreceptors located primarily on the low-pressure side of the circulation sense slight reductions in cardiac filling pressures and elicit sustained peripheral vasoconstriction. Because most inhalation and many intravenous anesthetics attenuate arterial baroreflex function, the low-pressure baroreflex may serve a major role in maintaining blood pressure during intraoperative hypovolemia. To activate the low-pressure baroreflex, progressive nonhypotensive reductions in central venous pressure were produced with graded applications of lower body negative pressure (LBNP, -5, -10, -15 mm Hg) in 18 ASA class I patients before elective surgery. This produced linear reductions in stroke volume as determined by impedance cardiography and cardiac output. Cardiopulmonary baroreflex-mediated increases in total and forearm vascular resistance assisted in maintaining stable blood pressure. After ten patients were anesthetized with fentanyl (12.5 μg/kg) and diazepam (0.25 mg/kg) and an additional eight received these agents plus supplemental N_2O (70%), reflex vasoconstrictor responses to LBNP were not attenuated and, therefore, blood pressure continued to be well maintained despite substantial reductions in cardiac filling pressures. Thus, these anesthetic regimens preserved vasoconstrictor responses mediated by cardiopulmonary baroreflexes. This promoted cardiovascular stability that may be particularly beneficial in patients with cerebral, cardiovascular, or renal disease undergoing surgical procedures with potential for rapid blood loss.

Key Words: RECEPTORS—pressoreceptors.
ANESTHETICS, INTRAVENOUS—fentanyl, diazepam.
ANESTHETICS, GASES—nitrous oxide

Cardiopulmonary baroreceptors located primarily on the "low-pressure" side of the circulation at the junction of the great veins and atria (1,2) sense slight decreases in central blood volume and initiate reflex increases in peripheral sympathetic efferent activity (3). This response results in immediate and sustained adjustments in peripheral vascular resistance (4) to maintain stable blood pressure until more gradual changes in renal function (5) and the renin–angiotensin system (6,7) occur to restore volume status.

The "high-pressure" arterial baroreflex is also a rapidly acting system that mediates changes in heart rate and peripheral resistance (4,8), but this reflex system is not activated until reductions in cardiac filling pressures are of sufficient magnitude to produce decreases in blood pressure (9). Furthermore, arterial baroreflex control of the heart is impaired by most all potent inhalational agents (10–12) and many intravenous agents (13–16). Thus, the low-pressure baroreflex system may be of primary importance for cardiovascular homeostasis during anesthesia and surgery.

Despite their potentially important role, little is known about the effects of anesthetic agents on the cardiopulmonary baroreflex system. An earlier study from our institution found that halothane markedly diminished low-pressure baroreflex control of peripheral resistance in humans (17). This effect resulted in precipitous decreases in blood pressure when anesthetized patients were exposed to controlled hypovolemia.

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In the present study, we examined the influence of fentanyl–diazepam anesthesia on reflex vasoconstrictor responses to mild, progressive reductions in cardiac filling pressures. These anesthetic agents were chosen because they are commonly used to combine the analgesic properties of fentanyl with the hypnotic and amnestic effects of diazepam. Although fentanyl and diazepam produce minimal alterations in cardiovascular function when employed individually (18–22), their combination is often associated with reductions in blood pressure, peripheral resistance, and plasma catecholamine levels (23,24). These responses are often undesirable and have been attributed to reduced peripheral sympathetic outflow (25). Based on this background, we hypothesized that the combination of fentanyl and diazepam in humans might diminish sympathetic vasoconstrictor responses mediated by cardiopulmonary baroreflexes. Such an effect might predispose patients to cardiovascular compromise during intraoperative blood loss. Furthermore, we conjectured that the addition of nitrous oxide to fentanyl–diazepam anesthesia might improve reflex vasoconstrictor responses because of its inherent sympathetic activating properties (26–28).

Methods

The investigation was approved by the Institution's Human Research Review Committee. Eighteen ASA class I unpremedicated subjects (23–37 years old) volunteered after informed consent was obtained to be studied before elective surgery. Heart rate, forearm blood flow, and arterial pressure were determined by ECG, Hg-in-Silastic strain gauge plethysmography, and radial artery cannulation, respectively. Central venous pressure (CVP) was monitored from a venous catheter inserted through the right external jugular vein. The position of this catheter in the intrathoracic region was confirmed by characteristic respiratory variations in the waveform.

Stroke volume was determined by impedance cardiography (29,30). We have previously described and validated this technique (30). Briefly, the method involves placement of four electrode bands circumferentially around the neck and thorax, application of alternating current (100 kHz, 4 mA) to the outer two electrodes, and measurement of changes in thoracic impedance from the inner two electrodes. Stroke volume and cardiac output calculated from noninvasive impedance waveforms correlate well with invasive measurements obtained with the Fick (31,32), dye (33–36), and thermodilution methods (37,38). However, the impedance method more accurately determines changes in stroke volume than absolute stroke volumes (30,33–35,38). Therefore, absolute values of stroke volume and calculated values of cardiac output and systemic vascular resistance provided in this report are relative estimates. The more precise changes (from baseline) in these variables depicted in Figures 2 and 3 are the critical values used to interpret the influence of fentanyl–diazepam ± N_2O anesthesia on cardiopulmonary baroreflex function.

Controlled central hypovolemia was produced with lower-body negative pressure (LBNP). This consisted of enclosing the body below the iliac crests in an airtight box. Subatmospheric pressure was created by an industrial vacuum source (noise insulated), controlled by a voltage regulator, and sensed by a vacuum gauge that had been previously calibrated against a mercury manometer. Forearm blood flow was determined by a temperature-compensated Hg-in-Silastic strain gauge and saddle (39). A venous occluding cuff was placed on the upper arm and an arterial occluding cuff placed around the wrist. Ten-second inflation curves were obtained at 20-second intervals (39). Airway CO_2 was monitored continuously by a mass spectrometer. Arterial blood pH, Po_2, and Pco_2 were measured by frequent arterial blood gas sampling.

Analog data were transcribed on a strip chart recorder and converted to digital format by hand analysis on a digitizing board on-line with a digital computer. Mean arterial pressure, cardiac output, and systemic and forearm vascular resistance were calculated.

Procedures

Subjects were supine throughout the study. Electrodes, forearm strain gauge, and arterial and venous catheters were placed, and 500 ml of colloid (6% hetastarch in 0.9% NaCl) was administered intravenously. This volume loading was precautionary. Our preliminary studies indicated that because many patients were mildly hypovolemic after the routine preoperation fasting, hypotension occurred in some volunteers on exposure to mild levels of LBNP. Subjects were positioned in the LBNP box, and a trial run was initiated to familiarize the volunteer with the procedure. Baseline recordings were obtained during three brief (10-second) relaxed end-expiratory breathholds (at 2-minute intervals). Lower-body negative pressure was applied in progressive 3-minute increments (-5, -10, and -15 mm Hg), and breathhold data

Table 1. Anthropometric and Arterial Blood Gas Values in Study Patients

	Fentanyl–diazepam		Fentanyl–diazepam–N_2O	
	Awake	Anesthetized	Awake	Anesthetized
Age (years)	32.3 ± 1.8*	—	28.8 ± 2.1	—
Height (cm)	179.6 ± 2.2	—	178.9 ± 1.9	—
Weight (kg)	79.6 ± 3.5	—	89.5 ± 3.7	—
pH	7.46 ± 0.04	7.40 ± 0.02	7.39 ± 0.03	7.41 ± 0.03
Po_2 (mm Hg)	98.3 ± 6.5	441.5 ± 24.6‡	94.2 ± 6.4	138.3 ± 8.7†
Pco_2 (mm Hg)	43.3 ± 2.1	36.1 ± 0.5	40.6 ± 2.1	39.7 ± 2.0

*Data are means ± SEM.
†,‡Significantly different from awake (control) responses at $P < 0.05$ or 0.01, respectively.

were obtained at the second and third minute of each LBNP level. Subjects then were preoxygenated with 100% O_2. Ten patients were anesthetized by IV administration of fentanyl (12.5 μg/kg) and diazepam (0.25 mg/kg) given simultaneously over 3 minutes. Ventilation was assisted and Pco_2 maintained constant by continuous mass spectrometer monitoring of end-tidal volumes. Eight additional patients were anesthetized in similar fashion, while nitrous oxide was gradually administered during the induction period until a 70% inspired concentration was achieved. Succinylcholine (1 mg/kg) was given before tracheal intubation. End-tidal Pco_2 was monitored continuously by mass spectrometer and kept constant at physiologic levels by assisted ventilation. Twenty minutes after intubation, baseline data were collected, and LBNP tests were repeated at identical intervals (and during end-expiratory apnea) as described for awake conditions.

Baseline data (before LBNP) were averaged, and the two readings at each LBNP level were averaged. Baseline hemodynamic variables while awake and anesthetized were compared by Student's *t*-tests for paired observations. Responses to LBNP were compared with analysis of variance. We assumed $P < 0.05$ to be significant.

Results

Age, height, and weight were similar in the two groups of study patients, as were arterial blood gas values in awake patients (Table 1). (Absolute values for all hemodynamic parameters derived during LBNP are available from the authors on request.) Po_2 was clearly elevated in both groups during anesthesia and was predictably higher in the fentanyl–diazepam group, because they received 100% O_2. While anesthetized, arterial Pco_2 was maintained at awake levels by controlled ventilation.

Table 2 provides the baseline hemodynamic data (before LBNP) in each group of patients while awake and approximately 20 minutes after establishing anesthesia. Fentanyl–diazepam anesthesia without N_2O did not alter cardiac index but resulted in significant decreases in total (systemic) and forearm vascular resistance that were associated with a 19% decrease in mean blood pressure. A similar (22%) significant decline in blood pressure occurred in the fentanyl–diazepam–70% N_2O group. However in the group receiving N_2O, this hypotension was not due to resistance decreases; rather, it was secondary to a 17% reduction in cardiac index associated with decreases in both heart rate and stroke volume index (Table 2). In addition, there was a significant 2 mm Hg increase in CVP in this group receiving supplemental nitrous oxide.

Progressive reductions in CVP occurred during step increases in LBNP (Fig. 1). These changes in CVP were similar in both groups while awake. However, CVP decreased less during fentanyl–diazepam–N_2O anesthesia ($P < 0.05$). Because reductions in CVP were different in the two groups and CVP is probably a more accurate index of the stimulus to low-pressure baroreceptors, hemodynamic responses were plotted in Figures 2 and 3 as a function of the change in CVP. Stroke volume index and cardiac index decreased progressively with LBNP, and neither anesthetic regimen altered this response. There was a slight but statistically significant bradycardia during LBNP after fentanyl–diazepam–N_2O anesthesia (Fig. 2).

Despite substantial reductions in CVP produced by LBNP, mean arterial pressure was not reduced (Fig. 3). Stable blood pressure was maintained by progressive increases in total and forearm vascular resistances. These resistance increases were not altered by either anesthetic regimen.

Discussion

The principal findings in these studies are that sympathetically mediated peripheral vasoconstrictor re-

Table 2. Baseline Hemodynamic Parameters (before LBNP) in Study Patients

	Fentanyl–diazepam		Fentanyl–diazepam–N_2O	
	Awake	Anesthetized	Awake	Anesthetized
HR (beats/min)*	66.8 ± 5.1†	63.1 ± 4.6	70.0 ± 3.5	64.9 ± 3.5‡
SVI (ml/m^2)	49.1 ± 2.3	52.8 ± 2.2	57.7 ± 3.2	49.2 ± 2.8‡, ‖
CI (L/min/m^2)	3.3 ± 0.4	3.3 ± 0.2	4.0 ± 0.4	3.3 ± 0.3‡, ‖
SP (mm Hg)	139.4 ± 3.7	111.0 ± 6.0§	136.0 ± 4.6	102.3 ± 4.4§
DP (mm Hg)	71.9 ± 2.0	58.6 ± 3.9§	75.5 ± 2.6	59.9 ± 2.5§
MABP (mm Hg)	94.4 ± 2.1	76.1 ± 4.5§	95.7 ± 2.9	74.0 ± 2.9§
TPRI *mm Hg* L/min/m^2	31.0 ± 3.3	24.1 ± 2.4‡	25.4 ± 2.4	23.9 ± 2.3 ‖
FBF (ml/min/100 ml)	4.5 ± 1.0	5.1 ± 0.9	5.5 ± 0.9	5.4 ± 1.2
FVR *mm Hg* ml/min/100 ml	33.3 ± 9.7	18.7 ± 3.5‡	23.5 ± 4.7	19.9 ± 4.0
CVP (mm Hg)	7.20 ± 1.49	6.36 ± 1.35	6.85 ± 0.64	8.78 ± 1.34‡, ‖

Data are means ± SEM.

†Abbreviations: HR, Heart rate; SVI, stroke volume index; CI, cardiac index; SP, DP, MABP, systolic, diastolic and mean arterial pressure (respectively); TRPI, total peripheral resistance index; FBF, forearm blood flow, FVR, forearm vascular resistance; CVP, central venous pressure.

‡,§Significantly different from response awake (control) values at $P < 0.05$ or 0.01.

‖ Change from awake response is significantly different between groups at $P < 0.05$.

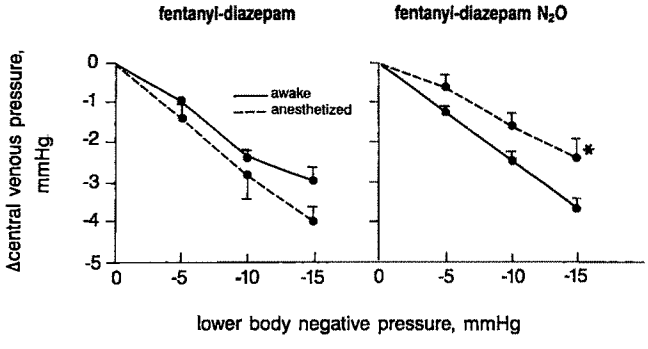

Figure 1. Lower body negative pressure provoked similar reductions in CVP in awake patients and in those anesthetized with fentanyl and diazepam alone. However, these reductions were attenuated in patients receiving N_2O. *$P < 0.05$.

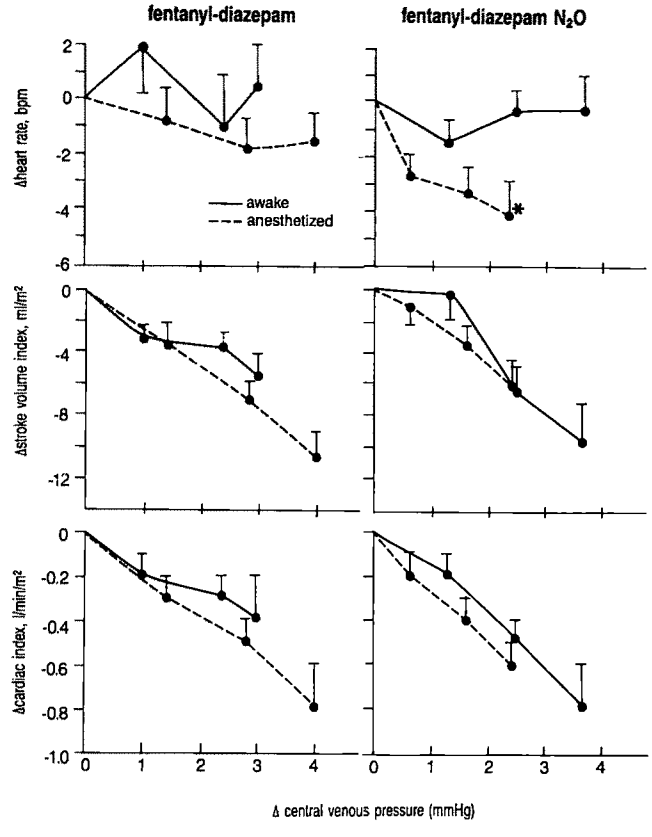

Figure 2. Hemodynamic responses to controlled reductions in CVP were similar (except for heart rate) in awake and anesthetized patients. A slight but significant bradycardia was observed during lower-body negative pressure in patients anesthetized with fentanyl–diazepam–N_2O. *$P < 0.05$.

sponses to nonhypotensive reductions of cardiac filling pressures are maintained in humans during fentanyl–diazepam and fentanyl–diazepam–N_2O anesthesia. This contrasts markedly to our previous work (17) that demonstrated that reflex peripheral vascular responses were blunted by halothane anesthesia. Our present data suggest that fentanyl–diazepam anesthesia as employed in this study may provide a margin of safety for surgical procedures in which rapid blood loss may occur by preserving reflex vasoconstrictor responses that are importantly involved in the maintenance of stable blood pressure during acute hypovolemia.

Baseline Hemodynamics

Fentanyl–diazepam anesthesia resulted in reductions in arterial pressure mediated by decreases in total (systemic) and forearm vascular resistance. These findings agree with a previous study by Tomicheck et al. (24), who infused graded doses of diazepam (0.125 to 0.5 μg/kg) 4 minutes before 50 μg/kg fentanyl (400 μg/min infusion) in cardiac patients with ejection fractions >50%. They found reductions in blood pressure, systemic vascular resistance, and plasma catecholamines. Flacke et al. (25) demonstrated that these anesthetics decrease sympathetic outflow from

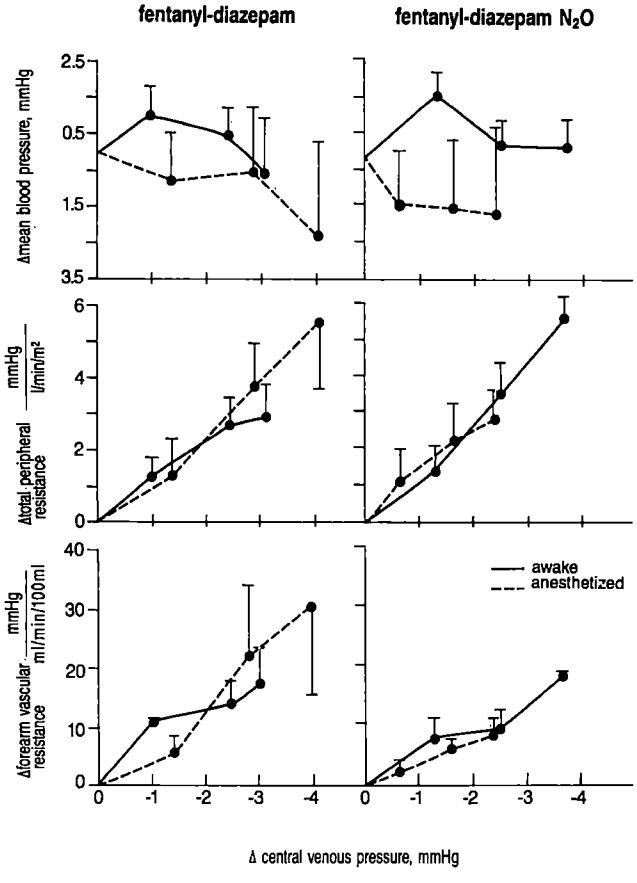

Figure 3. Reflex vasoconstrictor responses to reduced CVP were maintained during anesthesia. Therefore, blood pressure did not decline.

the central nervous system. Thus, the primary cardiovascular effect of fentanyl–diazepam anesthesia appears to be a reduction of peripheral sympathetic efferent nerve activity.

Evidence for a myocardial depressant effect of fentanyl–diazepam anesthesia is limited and not well supported. Large doses of fentanyl (50 μg/kg) and diazepam given to patients with mitral valve disease reduce cardiac function (23), and fentanyl–diazepam combinations used in pharmacologic doses on isolated rat hearts can diminish cardiac contractility (40). However, in our healthy patient population, low-dose fentanyl–diazepam anesthesia did not reduce cardiac index or increase CVP, which suggests that myocardial depression did not occur.

The addition of 70% N_2O to the anesthetic regimen corrected the reductions of total and forearm vascular resistance seen when fentanyl and diazepam were used alone. This effect is most likely due to the ability of nitrous oxide to activate the sympathetic nervous system (26–28). Despite this effect, blood pressures in anesthetized patients were lower than those recorded while awake. Hypotension was due to reductions in cardiac index. Nitrous oxide causes myocardial depression when combined with high-dose fentanyl (21,22) or diazepam (18) anesthesia. This depression is most exaggerated in patients with left ventricular dysfunction (41). In the present study, reductions in cardiac index produced by N_2O could partially be accounted for by reductions in heart rate, though stroke volume declined and CVP increased, which indicates some impairment of cardiac function.

Responses to LBNP

Graded applications of LBNP produced progressive reductions in CVP in both awake and anesthetized patients. Reductions in CVP tended to be greater when LBNP was used in patients anesthetized with fentanyl–diazepam alone. In contrast, however, these CVP reductions were significantly less in the anesthetized patients receiving N_2O (Fig. 1). This may be due to a reduced venous compliance secondary to an increased sympathetic activity in venous beds produced by N_2O (39). This could have attenuated caudal venous blood pooling during LBNP. Because of these apparent differences in sequestration of blood, we chose to plot hemodynamic responses to LBNP as a function of the reductions in CVP. These changes are probably more specific for the actual stimulus (decreased stretch) at cardiopulmonary baroreceptor sites than the absolute level of LBNP.

Progressive reductions in cardiac filling produced graded decrements in stroke volume and cardiac output. These responses were virtually identical in both groups of patients while awake and anesthetized. There was, however, a slight but significant bradycardia (3–4 beats/min) during LBNP in the fentanyl–diazepam–N_2O group, which may be attributed to the nitrous oxide (28).

In awake patients, the substantial reductions in stroke volume and cardiac output produced by LBNP did not result in hypotension. Furthermore, tachycardia did not occur. Thus, high-pressure arterial baroreceptor reflexes were probably not activated; resistance changes were mediated primarily by cardiopulmonary baroreflex mechanisms.

Our previous work in humans anesthetized with halothane demonstrated significant decreases in blood pressure during low-level LBNP. This hypotension occurred because cardiopulmonary baroreflex-mediated vasoconstriction was markedly attenuated by halothane (17). In the present study, reflex vasoconstrictor responses provoked by unloading cardiopulmonary baroreceptors were maintained during

fentanyl–diazepam ± N_2O anesthesia and, therefore, hypotension did not occur. These findings emphasize the critical role of the low-pressure cardiopulmonary baroreceptor reflex for maintaining blood pressure during reductions in cardiac filling pressures.

The remarkable conservation of reflex vasoconstrictor responses during fentanyl–diazepam anesthesia was somewhat unexpected. These agents have been shown to reduce central sympathetic outflow when employed in combination (25). We speculated that sympathetically mediated reflex vasoconstrictor responses would also be diminished. They were not. In addition, we conjectured that the sympathetic activation associated with administration of N_2O (26–28) might enhance reflex vasoconstrictor responses. It did not. Although the mechanism(s) involved in the maintenance of reflex vasoconstriction during fentanyl–diazepam anesthesia with and without N_2O is not known, one possible explanation may be that baroreflex responses mediated through lower brain stem regions may be preserved independent of alterations in baseline sympathetic outflow from higher CNS centers. Other unexplored but potential mechanisms for these effects include sensitization of low-pressure baroreceptors by these anesthetics or enhanced preganglionic, ganglionic, and postganglionic transmission of sympathetic impulses, and/or enhanced release of neurotransmitters from nerve terminals.

In summary, the present study demonstrates that low-dose fentanyl–diazepam anesthesia with or without N_2O does not diminish low-pressure cardiopulmonary baroreflex-mediated vasoconstrictor responses to hypovolemia. Reflex systemic and forearm vasoconstriction were similar in awake and anesthetized patients when exposed to LBNP. We have previously shown that this anesthetic regimen also preserves arterial baroreflex-mediated slowing of heart rate in response to hypertensive stimuli (14). These combined findings indicate that fentanyl–diazepam anesthesia (with or without N_2O) promotes cardiovascular stability by maintaining high- and low-pressure baroreflex responses to increased afterload or decreased preload. This suggests that these anesthetic combinations may be ideal for surgical procedures with potential for rapid blood loss in patients at risk for cardiovascular, renal, or cerebral compromise. We qualify this by pointing out that the baseline reductions in blood pressure produced by these anesthetic combinations must be taken into consideration on establishing surgical levels of anesthesia. Careful volume loading before anesthetic induction may be necessary to help maintain stable preoperative cardiovascular status. In addition, one must consider the myocardial depressant effect of the addition of nitrous oxide to these anesthetics in the patient with limited cardiac reserve.

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Height, Weight, and the Spread of Subarachnoid Hyperbaric Bupivacaine in the Term Parturient

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NORRIS MC. Height, weight, and the spread of subarachnoid hyperbaric bupivacaine in the term parturient. Anesth Analg 1988;67:555–8.

Using a standardized technique, spinal anesthesia was induced in 50 term parturients to study the correlation between patient height, weight, and body mass index (BMI) and the spread of sensory blockade. All patients received 12 mg hyperbaric bupivacaine while in the right lateral decubitus position on a horizontal operating table. Immediately after drug injection, the women were turned to the supine horizontal position with left uterine displacement. Fifteen minutes after drug injection, the level of analgesia to pinprick was measured. Linear regression analysis revealed no significant correlation between height (146–175 cm), weight (57.3–93.6 kg), or body mass index (21–38 kg/m^2) and the spread of spinal anesthesia (T7–C8). It is concluded that, in term parturients, patient height, weight, or BMI does not significantly affect the spread of hyperbaric spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHESIA—obstetric.

Subarachnoid local anesthetics provide rapid and profound anesthesia for cesarean section. Greene (1) states that "common sense" and "clinical experience" indicate that the same dose of local anesthetic will produce a higher level of neural blockade in a short patient than in a tall patient. Indeed, most authors recommend varying the dose of local anesthetic depending on patient height (2,3). However, there are few objective data available to support this practice. We undertook this study to determine how patient height affects the spread of spinal anesthesia in the parturient.

Recent data suggest that patient weight and body mass index (BMI) may alter the spread of isobaric local anesthetic solutions in the subarachnoid space (4). We also studied the influence of these parameters on the subarachnoid spread of hyperbaric local anesthetic solutions.

Methods

The institutional review board approved our protocol. We studied 50 healthy laboring and nonlaboring term parturients consenting to spinal anesthesia for cesarean section. On a horizontal operating table, the patients assumed the right lateral decubitus position with their head supported by a pillow. We inserted a 25- or 26-gauge needle into the subarachnoid space at the L2–3 or L3–4 interspace and injected 12 mg 0.75% bupivacaine with 8.25% dextrose (1.6 ml) over 5–10 seconds without barbotage. We then turned the patients supine and tilted the operating table to the left to establish uterine displacement. The operating table remained horizontal throughout the study. After 15 minutes, we measured the level of analgesia to pinprick bilaterally in the midaxillary line and down the arm. After injection of hyperbaric bupivacaine in term parturients, a detectable level of analgesia occurs within 2–4 minutes and promptly ascends. The maximum level occurs by 10–12 minutes and is stable for at least 45 minutes (M.C. Norris, unpublished data). We also recorded the height and weight of each patient. We used a linear regression analysis to correlate spread of blockade with height, weight, and BMI (wt/ht^2).

Results

Our 50 patients ranged from 146 to 178 cm in height and weighed between 57.3 and 93.6 kg. All anesthet-

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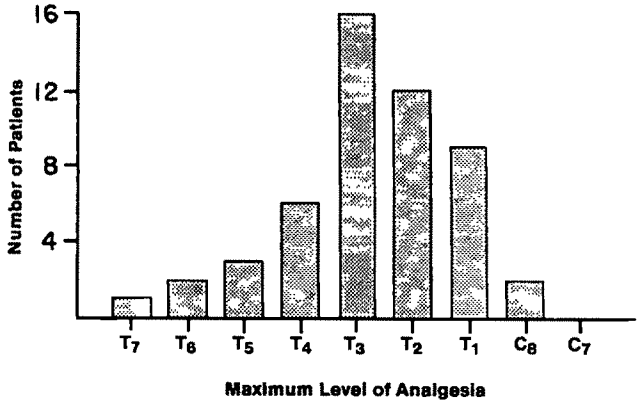

Figure 1. Maximum level of analgesia to pinprick, measured 15 minutes after injection of 12 mg hyperbaric bupivacaine in 50 supine term parturients.

ics were adequate for cesarean section with levels of analgesia ranging from T7 to C8 with a median level of T3 (Fig. 1). Neither height, weight, nor BMI correlated significantly with the spread of subarachnoid blockade (Figs. 2–4, Table 1).

Discussion

Using glass tubes and methyl violet dye, Barker (5) showed that hyperbaric local anesthetic solutions pool in dependent sections of the spinal column. Subsequently, Kitahara et al. (6) showed that radiolabeled hyperbaric local anesthetics move by bulk flow with gravity to dependent areas of the spine. Kitahara et al. (6) then correlated the spread of these solutions with the spread of analgesia. In the supine position, the upper lumbar and lower thoracic vertebrae slope 8 to 12° in the cephalad direction (7). Thus, hyperbaric local anesthetic solutions pool in the lowest part of the thoracic spine (T5–T6), regardless of the height of the patient (5,6).

However, Greene (1) argues that taller patients have longer and larger subarachnoid spaces with more CSF volume. Therefore, local anesthetics should reach a lower dermatomal level after traveling the same distance from the site of injection. In addition, the greater volume of CSF would dilute the injected drug and limit the area exposed to minimum blocking concentrations. Both of these effects would limit the spread of blockade in taller patients.

Clinical studies shed little light on this subject. Moore (8) claims a very significant relation between height and spread of blockade after 7.5 mg hyperbaric bupivacaine or 12 mg hyperbaric tetracaine. However, he presents no data to support this conclusion. Similarly, a more recent study (9) claims a significant inverse relation between level of analgesia and height in patients between 153 and 193 cm tall. Patients in this study received 15 mg hyperbaric 0.5% bupivacaine and developed sensory levels ranging from T9 to C8 (mean T4). On the other hand, men and women receiving 10 or 15 mg hyperbaric tetracaine had the same level of analgesia (T8–T9) despite the greater height of the men (173 cm vs 160 cm) (10).

In this, the first study of this issue in pregnant women, we are unable to demonstrate any correlation between level of blockade and patient height. Our results, like those of Barker (5) and Kitahara et al. (6) suggest that in supine patients hyperbaric local anesthetic solutions flow to the dependent area of the thoracic spine and achieve similar levels of blockade regardless of patient height. Alternatively, the small influence of height on spread of blockade noted in nonpregnant patients (8,9) may be obscured in pregnant patients by the increased sensitivity to local anesthetic action seen in pregnancy (11). If a correlation does exist between patient height and blockade, it is probably minor (1,9) and of clinical importance only in children (1). The 95% confidence limits of our data (2 × standard error of estimate) suggest that any correlation between height and the spread of blockade must be less than six segments per meter. Therefore, the largest possible difference in blockade over usually encountered heights (1.46–1.76 m) would be two segments, not a clinically significant difference given the wide spread of final dermatome levels at any given height (Fig. 2).

This study was performed with hyperbaric bupivacaine. Studies in nonpregnant patients have shown that hyperbaric solutions of tetracaine and bupivacaine behave similarly (12). Thus, our results probably also apply to hyperbaric tetracaine solutions and possibly to all hyperbaric local anesthetic solutions.

The spread of isobaric bupivacaine appears to be significantly influenced by patient weight and BMI (4,9). However, both our results and those of Pitkanen (9) demonstrate no correlation between spread of hyperbaric bupivacaine and weight. The maximum spread for increases in height not detectable in this study would be an increase in level of 0.04 segment per kilogram. Thus, over the 50-kg weight range commonly encountered in clinical practice, there may be a two-segment rise in block; once again, not a clinically significant difference. Our data and Pitkanen's (9) do suggest a weak trend toward higher levels of anesthesia with increased body mass index. With our data an undetected rise in sensory blockade with increasing BMI of 0.12 segment/kg/m^2 could exist. Clinically, the average height of blockade would increase from T4 in a parturient with a BMI of 20 kg/m^2 to T2 in one with a BMI of 37

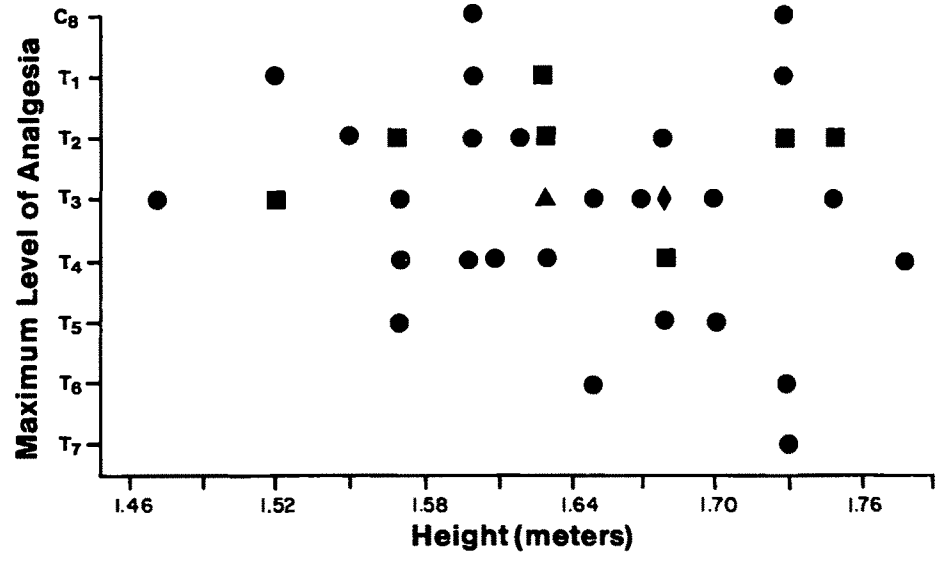

Figure 2. Relation between height and maximum cephalad spread of blockade after 12 mg hyperbaric bupivacaine in 50 term parturients. Symbols: ●, one patient; ■, two patients, ▲, three patients; ◆, four patients.

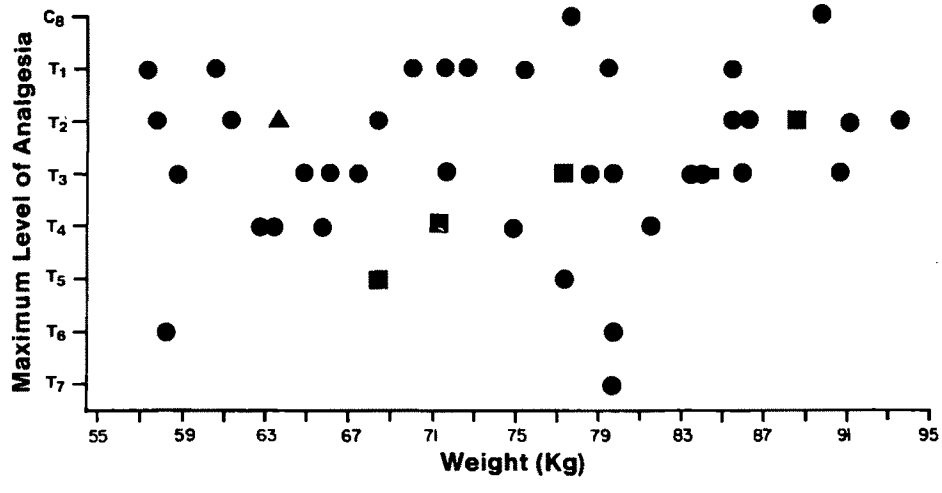

Figure 3. Relation between weight and maximum cephalad spread of blockade after 12 mg hyperbaric bupivacaine in 50 term parturients. Symbols as in Figure 2.

kg/m^2. Thus, for two patients of the same height, the heavier one may have a slightly higher sensory level. This effect may also have an anatomic basis as the larger buttocks of the obese patient may increase the slope of the lumbar thoracic spine and encourage cephalad spread of subarachnoid local anesthetics.

Our results directly apply only the patients within the height and weight ranges studied. However, these ranges encompass the majority of commonly encountered parturients. Probably at some height <146 cm (4'11"), 12 mg bupivacaine would result in an excessive level sensory analgesia. In patients taller than 178 cm (5'8"), we speculate that an adequate sensory would still be obtained but at some height the increased volume of the subarachnoid space would eventually dilute the local anesthetic enough to prevent sensory blockade of adequate intensity from developing. We routinely achieve similar sensory levels of analgesia after a standard dose of hyperbaric bupivacaine in more obese parturients. However, we usually perform the block with these patients sitting rather than lying on their side, and these data are not included in this study.

In summary, in parturients within commonly encountered ranges of height and weight, the spread of sensory blockade after subarachnoid hyperbaric bupivacaine does not correlate with the height or weight of the patient. This finding greatly simplifies clinical practice: a single dose of local anesthetic (i.e., 12 mg hyperbaric bupivacaine) provides adequate anesthesia for cesarean section regardless of the height or weight of the usual parturient. In nonpregnant patients, the relation between height and spread of spinal anesthesia requires further study to resolve current uncertainties (8,9).

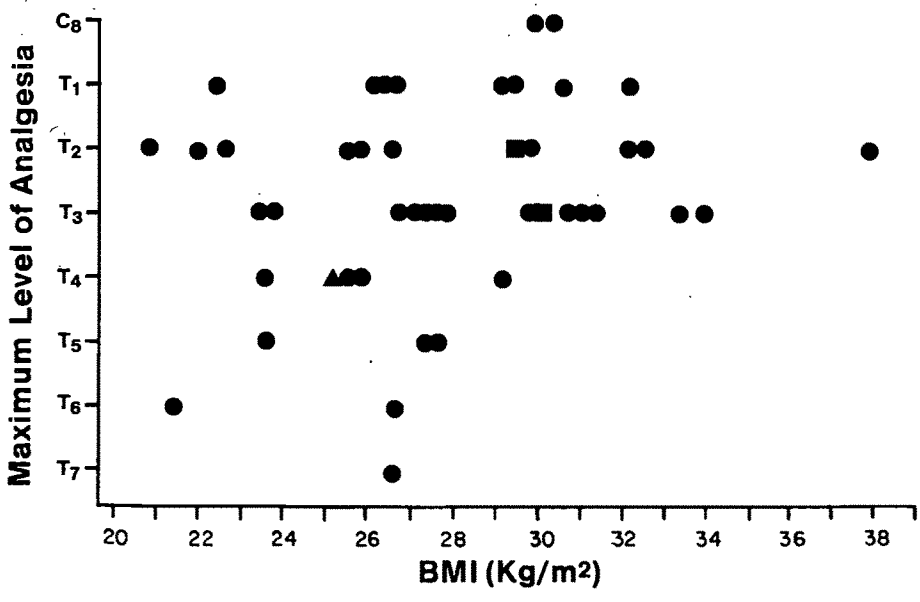

Figure 4. Relation between BMI and maximum cephalad spread of blockade after 12 mg hyperbaric bupivacaine in 50 term parturients. Symbols as in Figure 2.

Table 1. Linear Regression: Spread on Sensory Blockade

Variable	Intercept	Slope	Standard error of estimate	r	*P* Value
Height	C-2	−4.4 seg/m	±2.87 seg/m	0.21	0.15
Weight	T-4	0.02 seg/kg	±0.02 seg/kg	0.12	0.41
BMI	T-6	0.11 seg/kg/m^2	±0.06 seg/kg/m^2	0.20	0.06

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Comparison of Continuous Epidural Infusion of Fentanyl–Bupivacaine and Morphine–Bupivacaine in Management of Postoperative Pain

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FISCHER RL, LUBENOW TR, LICEAGA A, McCARTHY RJ, IVANKOVICH AD. Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. Anesth Analg 1988;67:559–63.

The short duration of epidural fentanyl has limited its direct comparison with epidural morphine in previous reports. The following study was performed of continuous postoperative epidural infusions at 5 ml/hr fentanyl 10 μg/ml (n = 59) or morphine 0.1 mg/ml (n = 48), both with bupivacaine 0.1%, in patients having cesarean sections. Postoperative evaluations included the frequency and magnitude of clinically evident respiratory depression, the adequacy of analgesia, nausea, pruritis, the ability to ambulate, and other side effects for 24 hours. Analgesia and the number of supplemental narcotic injections needed were similar in both groups. The incidence of nausea and pruritis was significantly less in the patients receiving fentanyl. No patient developed respiratory depression in either group. Patient and staff acceptance of the continuous epidural technique was excellent because there were only minor catheter-related problems associated with its use. It is concluded that continuous epidural fentanyl combined with bupivacaine offers excellent postoperative analgesia with minimal side effects.

Key Words: PAIN—postoperative. ANESTHETIC TECHNIQUES, EPIDURAL—fentanyl, morphine. ANALGESICS—morphine, fentanyl

The epidural injection of morphine is an effective method for management of postoperative pain. The associated side effects have, however, precluded its widespread use in a variety of clinical settings (1–3). Agents with greater lipophilicity such as fentanyl have been utilized in an attempt to avoid some of these side effects, but the short duration of action of fentanyl has been a limitation (4,5).

At our institution, continuous postoperative epidural infusions of both morphine and fentanyl have been in use for several years (6,7). In addition, our practice has evolved to combine low concentrations of these narcotics with dilute solutions of local anesthetics. This has served to decrease the doses of narcotics and local anesthetics with apparent minimization of side effects.

The present study was performed to quantitate and compare prospectively under controlled conditions, in a randomized double-blind fashion, the efficacy and safety of the continuous epidural infusion of morphine or fentanyl in combination with low concentrations of a local anesthestic in the management of postoperative pain.

Methods

The study was approved by the Medical Center Human Investigation Committee. Informed consent was obtained from 107 ASA physical status I and II patients scheduled to undergo cesarean section. Patients were randomized in a double-blind fashion to one of two treatment groups by the pharmacy at the time the patient entered the study. Patients in group 1 were given epidural infusions of morphine sulfate 0.01% in bupivacaine 0.1%; patients in group 2 received fentanyl 0.001% in bupivacaine 0.1%. All

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patients had epidural anesthesia to the fourth thoracic dermatomal level for their surgery using lidocaine 2% with epinephrine 1:200,000.

A continuous epidural infusion of the study drug was started immediately postoperatively at a rate of 5 ml/hr after a 5-ml bolus of the solution. The infusion was given via an IMED (model 960) infusion pump. A 100-ml in-line reservoir was placed between the bag containing the solution and the IMED infusion pump. No more than 10 ml of epidural solution was placed in the reservoir so no more than 10 ml could be given inadvertently as a bolus. Patients needing additional pain medications for pain relief were given IM meperidine. Patients were encouraged to ambulate and those requiring treatment for nausea or pruritis were given oral benztropine mescylate or IM diphenhydramine, respectively. All patients had urethral catheters in place during the first postoperative day. The epidural catheters were withdrawn after 24 hours at the conclusion of the study.

The postoperative study recorded included assessment of pain relief according to a visual analog scale, the amount and number of supplemental meperidine injections received, ambulatory status, the number of diphenhydramine and benzytropine injections and a subjective assessment of any buttock numbness or leg weakness. Any incidence of apnea or mental status changes associated with respiratory depression were also noted. Data collection started in the recovery room after initial drug injection and continued every 4 hours thereafter for 24 hours. Respiratory rates, vital signs, and mental status were assessed hourly. Pain scores and respiratory rates were analyzed by two-way ANOVA with one repeated measure. The remainder of the data were analyzed using Fischer's exact test. A P value of 0.05 was considered statistically significant.

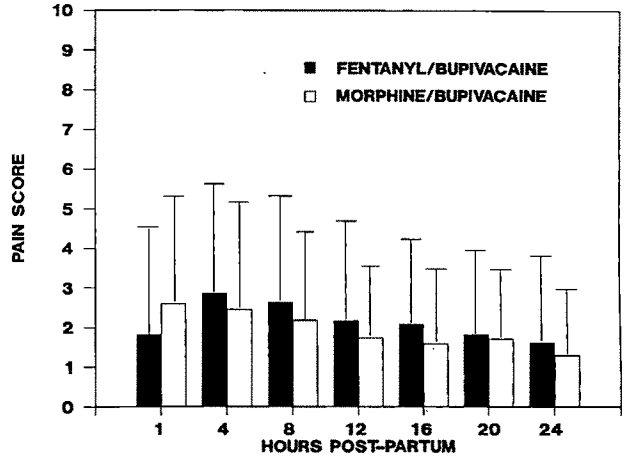

Figure 1. Visual analog pain scores during the first 24 postoperative hours (mean ± SD).

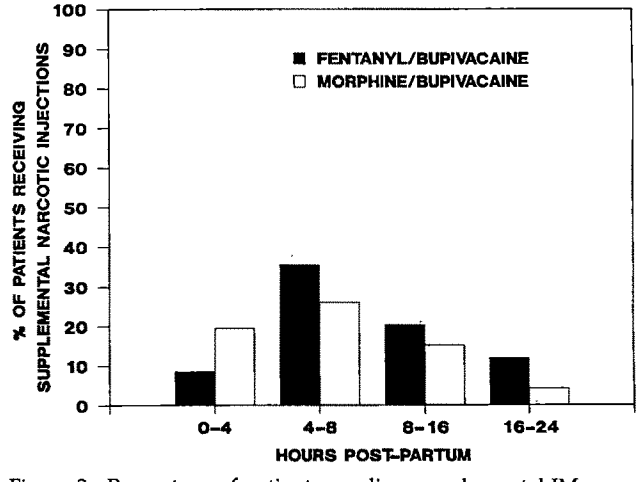

Figure 2. Percentage of patients needing supplemental IM meperidine injections at each of the 4-hour postpartum intervals; 17% of patients given morphine sulfate with bupivacaine and 15% of those given fentanyl with bupivacaine required supplemental meperidine in more than one time period.

Results

One hundred seven women participated in the study: 59 patients in the fentanyl–bupivacaine group and 48 in the morphine–bupivacaine group. One patient was removed from the study because of side effects (see later). There were no significant differences between the two groups in age, race, socioeconomic status, weight, or height.

The degree of analgesia achieved was similarly satisfactory in all patients in both groups (Fig. 1). The need for supplemental meperidine was similar in the two groups (Fig. 2). All patients expressed satisfaction with the degree of analgesia.

Pruritis requiring treatment with IM diphenhydramine occurred significantly less often in the fentanyl/bupivacaine group (22%) than in the morphine–bupivacaine group (42%) (Fig. 3). One patient in the morphine–bupivacaine group complained of pruritis so severe that she had to have her epidural removed and was thus lost from the study.

The incidence of nausea was also significantly lower in the fentanyl group (3.4%) as compared with the morphine group (17.4%) (Fig. 3). Urinary retention could not be evaluated due to presence of urethral catheters. Time to ambulation was similar in both groups, as was the incidence and location of leg weakness and buttock numbness (Table 1). There were no major or minor technical problems in any patient and in no case did respiratory depression develop.

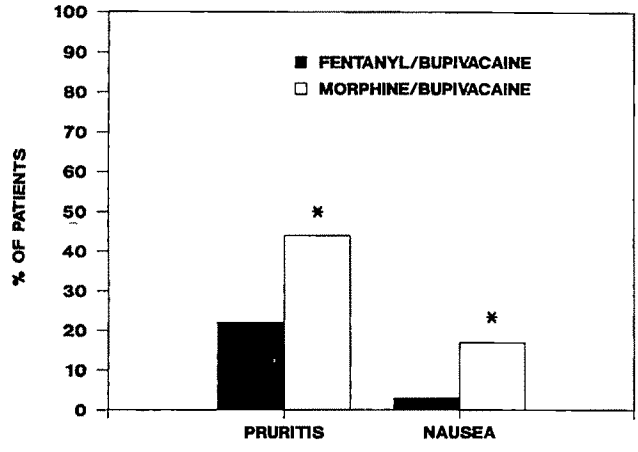

Figure 3. Percentage of patients developing pruritis or nausea during the 24-hour study period. An asterisk denotes a statistically significant difference ($P = 0.03$).

Discussion

Previous reports have documented the efficacy of both epidural fentanyl and morphine in the relief of postoperative pain (4,5). However, in these studies the short duration of fentanyl did not permit comparison between morphine and fentanyl regarding degree of analgesia and the incidence of side effects because administration was by bolus injection. As shown in our study, a continuous infusion technique circumvents the problem of the short duration of bolus fentanyl and provides the opportunity to observe significant clinical differences between epidural fentanyl and morphine. The present study also supports the clinical impression that combinations of narcotics with local anesthetics can provide excellent pain relief. Several authors have suggested that these combinations may produce a synergistic effect, while reducing the incidence of side effects (8–12).

Important differences between epidural fentanyl and morphine have emerged from this investigation. The incidence of pruritis was 48% less and the incidence of nausea 80% less with epidural fentanyl than with epidural morphine. The higher lipophilicity of fentanyl may be responsible for the observed lower incidence of side effects. Because fentanyl is more lipophilic, it partitions itself into lipid containing structures of the spinal cord and epidural fat, thereby allowing less free fentanyl to migrate into the CSF with less rostral spread to the brain. Morphine, in contrast, is more hydrophilic and following epidural injection more drug is partitioned into the CSF allowing it to spread rostrally to the subependymal cells of the fourth ventricle with possible associated side effects.

The method of delivery of drug to the epidural space may also be important in reducing side effects. With our continuous epidural infusion technique the number of molecules of narcotic within the CSF at any one time is less than that with bolus epidural injections, thus allowing the spinal cord and epidural fat to act as more effective drug reservoirs. Although this lipophilic depot may serve as a safety valve to minimize the rostral spread, it may become saturated after large boluses of fentanyl. For example, a 100-μg fentanyl bolus has no effect on end-tidal P_{CO_2}, resting ventilation, or the ventilatory response to inhaled CO_2 (13). Increasing the epidural dose to 200 μg fentanyl produces no change in end-tidal P_{CO_2} or respiratory rate, but does depress the ventilatory response to inhaled CO_2 (14), suggesting that the lipid structures of the spinal cord and epidural fat can be saturated and overcome by increasing the dose of fentanyl. With morphine, on the other hand, an epidural bolus dose of as little as 2 mg can depress minute ventilation while respiratory rate and end-tidal P_{CO_2} remain unchanged (15). The more hydrophilic morphine has no "reservoir" serving as a safety valve, and even a small bolus may produce clinical respiratory depression. Because respiratory depression is a dose-dependent phenomenon and morphine 2 mg and fentanyl 200 μg probably represent the threshold doses, fentanyl has a higher therapeutic index and is thus inherently safer because there is less rostral spread. This has been borne out by previous studies in which there have been no cases of clinically significant respiratory depression with epidural fentanyl (5,13). Selection of the infusion rate for fentanyl that we used in the present study followed from previous authors' published experience and was based on the observation that the continuous infusion of epidural fentanyl at 60 μg/hr (16) or 1–2 $\mu g^{-1} \cdot kg^{-1} \cdot hr$ (17) is both safe and effective.

A previous study from our institution demonstrated a reduction in the side effects with a continuous epidural infusion as compared with a bolus technique (7). In the present study of a continuous infusion technique, the incidence of side effects was also lower than the incidence reported by others where bolus techniques were used. Pruritis, for example, occurs in as many as 90% of patients when a 10-mg morphine bolus is given epidurally (18). This contrasts with our study in which approximately one-third of patients given epidural morphine and one-sixth of the patients given epidural fentanyl developed pruritis.

The safety of epidural narcotic infusions was also demonstrated in the present study: no patient suffered from clinically significant respiratory depression. Indeed, the method used for postoperative pain relief in the present study has been used in postop-

Table 1. Respiratory Rates and Side Effects after Continuous Epidural Infusions

	Respiratory rates									
	Time postoperative (hours)									
	0	1	2	3	4	8	12	16	20	24
Fen/Bup and MS/Bup ±SD	20.6 ±2.5	20.4 ±2.2	20.4 ±1.6	20.1 ±1.8	20.1 ±2.1	20.4 ±1.9	20.3 ±2.2	20.3 ±1.9	20.4 ±1.5	20.8 ±1.8

	Incidence (%)			
	Time postoperative (hours)			
Side effects	0–4	4–8	8–16	16–24
Mental status (alert, oriented)				
Fen/Bup (n = 59)	91	100	98	100
MS/Bup (n = 46)	98	95	100	100
Ambulatory				
Fen (n = 59)	22	30	42	58
MS (n = 46)	13	35	52	65
Leg weakness				
(37% 22/59)†				
Fen (n = 59)	22	15	17	20
Location				
Right	23	22	40	33
Left	15	44	30	42
Both	61	33	30	25
(56% 26/46)†				
MS (n = 46)	39	19	28	26
Right	1	33	54	33
Left	22	44	31	42
Both	72	22	15	25
Buttock numbness				
(61% 36/59)†				
Fen (n = 59)	37	25	32	37
Location				
Right	9	40	37	45
Left	14	20	10	32
Both	77	40	53	23
(74% 34/46)†				
MS (n = 46)	54	24	43	39
Location				
Right	20	18	35	33
Left	20	36	35	28
Both	60	46	30	39

Abbreviations: Fen, fentanyl; Bup, bupivacaine; MS, morphine sulfate.
†Percentage of patients in the group complaining of leg weakness or buttock numbness at any time.

erative patients for several years in the setting of a standard hospital ward where routine postoperative care is normally given. The use of apnea monitors is not required; nursing observation of respiratory rate every hour has been found to be safe and appropriate monitoring for side effects and complications of epidural narcotics where given by a continuous infusion.

Other authors have used respiratory rate monitoring and found it to be an adequate measure of clinical respiratory depression. In a previous investigation, respiratory rate monitoring was utilized with 125 patients on hospital medical and surgical wards receiving multiple epidural injections of morphine 2–5 mg at 12-hour intervals for 3 days (19). The authors concluded that respiratory rate monitoring by nursing personnel would detect clinically significant respiratory depression. We admit, as they noted, that respiratory rate monitoring alone will not detect subclinical respiratory depression, but that is not necessary because subclinical respiratory depression will not be treated with naloxone. In another study, 276 patients receiving postoperative epidural morphine analgesia were evaluated with respiratory rate monitoring to detect respiratory depression. With this modality they noted that no one had a respiratory rate less than 10 breaths/min, but did detect one

patient who was unusually somnolent after epidural injection. This patient's somnolence was reversed with naloxone (20). In these studies apnea monitoring or ICU observation was not needed because clinical respiratory depression was not observed and indeed the only side effect noted, somnolence, was detected by direct clinical observation.

This approach to the postoperative management of pain, of not requiring a stay in an intensive care unit, allows for broad acceptance of the technique by physicians, nurses, and patients. In our institution over 3000 cases of continuous epidural infusions of narcotic–local anesthetic mixtures have been performed without an instance of apnea or respiratory depression.

The presence of numbness or paresthesias in the buttocks or legs was similar in the two groups in the present study. Numbness or paresthesias being primarily due to sensory blockade by the local anesthetic, no intergroup differences were to be expected. The relatively high overall incidence of buttock numbness (61%) and leg weakness (74%) in this study as compared with our previous experience with continuous epidural infusion (6–8) may be a result of a residual effect of the intraoperative epidural anesthetic with 2% lidocaine or due to hormonal or mechanical potentiation of local anesthesia in pregnant patients.

In conclusion, the epidural infusion of fentanyl has significant advantages over epidural morphine for relief of postoperative pain. The combination of dilute local anesthetic with fentanyl or morphine provides high-quality analgesia with minimal side effects. The continuous infusion technique also obviates the need for repetitive bolus injections, while providing a constant level of analgesia.

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The Effect of Halothane, Enflurane, and Isoflurane on RNA Synthesis in Isolated Rat Liver Cell Nuclei

Christine Bastian, MD

BASTIAN C. The effect of halothane, enflurane, and isoflurane on RNA synthesis in isolated rat liver cell nuclei. Anesth Analg 1988;67:564–9.

The effect of halothane, enflurane, and isoflurane inhaled in vivo on the in vitro transcription in isolated liver cell nuclei was studied in female Wistar rats. After 0.45–0.48 MAC of any of the three anesthetics in oxygen for 18 hours, in vitro RNA synthesis increased, a maximum being found on the third day after inhalation of halothane, on the second day in enflurane, and immediately after cessation of inhalation in the case of isoflurane. A similar stimulation of RNA synthesis was observed in rats given phenobarbital in the drinking water. The possibility that the observed increase in the transcription rate is related with enzyme induction is discussed.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane, isoflurane. METABOLISM, RNA SYNTHESIS—halothane, enflurane, isoflurane. LIVER—RNA synthesis.

Several authors have described inhibition of cell division by volatile anesthetics (1–3). Furthermore, a reduced incorporation of the respective precursors into DNA, RNA, and proteins has been observed in vitro in the presence of anesthetics (4–7). Conklin and Lau (8–10) investigated the effects of halothane and enflurane on Tetrahymena pyriformis and found a diminished uptake of radioactively marked precursors in DNA, RNA, and proteins, as well. However, when isolated cell nuclei of the protozoon were incubated with the four nucleosid triphosphates in the presence of halothane or enflurane, no inhibition of the DNA or RNA synthesis took place. From this the authors concluded that inhalation anesthetics do not influence the reaction of the DNA or RNA polymerase.

Because the above mentioned studies mainly dealt with cell cultures and unicellular organisms and because the anesthetics were administered in vitro, it seems to be justified to apply today's most frequently used volatile anesthetics, halothane, enflurane, and isoflurane in vivo, and to study their effects on the reaction of the RNA polymerase under in vitro conditions.

The anesthetics in this study were administered by inhalation in concentrations in O_2 of about 0.45–0.48 MAC for rats (11), concentrations less than those usually used under clinical conditions to permit the longest possible time of exposure without killing the rats, while still delivering high total amounts of anesthetics (MAC – hours). Anesthetics were administered in 100% O_2 to assure oxydative conditions even in the presence of a moderate respiratory depression.

To study the reaction of the RNA polymerase, isolated nuclei of liver cells were utilized, because the liver plays a dominating role in the biotransformation of anesthetics (12,13). Isolated cell nuclei preserve the capability of synthesizing RNA in vitro for some period of time. When incubated in a suitable medium in the presence of homologous cytosol, the RNA polymerase I (for the synthesis of r-RNA) as well as the RNA polymerase II (for the synthesis of m-RNA) remain active. Interactions of nucleus and cytoplasm, which influence gene expression, also remain effective (14,15).

Material and Methods

The investigations were approved by our authorized animal welfare observer. Female Wistar rats (Bor:

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W/SW) weighing 140 to 160 g were used for the studies. They were kept five to a cage in air-conditioned rooms with a temperature of 22 ± 2°C and a relative humidity of 50–60%. The light/dark rhythm was 12 hours; the nutrition consisted of water ad libitum and Altromine 1324. Every eight rats were exposed to an appropriate mixture of O_2 and anesthetic in an airtight glass chamber of 20-L volume. Using a Dräger anesthetic apparatus (Sulla 808 V), the circle system of which was linked with the inlet of the glass chamber via a connecting tube, halothane, enflurane, or isoflurane were introduced into the glass chamber using a Dräger 19.9 vaporizer with an oxygen flow of 1.6 L/min for 18 hours. To prevent the escape of anesthetics into the room, the glass chamber was equipped with an outlet opening on the top that was placed beneath a laboratory hood with a flue. The concentration of anesthetics in the chamber was monitored with a mass spectrograph Airspec MGA 2000. After about 20 minutes the mixture of O_2 and anesthetic was equilibrated in the chamber. After 18 hours the rats were taken out of the glass chamber and returned to their cages. Every 24 hours two rats were killed by CO_2, the livers removed, and the cell nuclei isolated. Untreated rats and those only exposed to an oxygen flow of 1.6 L/min in the glass chamber for 18 hours served as controls. Four hours before the application of the anesthetics, the food but not the water was withdrawn from the rats' cages.

Another group of rats, kept under the earlier-described conditions, were given 1 g phenobarbital with every liter of drinking water for 7 days. Two of these rats at a time were killed by CO_2 for several days after the start of the administration of phenobarbital, and the livers removed for the cell nuclei preparations for evaluating in vitro transcription (see later). Halothane was obtained from ICI-Pharma, enflurane, and isoflurane from the Deutsche Abbott GmbH, and phenobarbital (Luminal) from the BAYER AG.

Preparation of Cell Nuclei and Cytoplasm

Nuclei were isolated from the liver of female Wistar rats (weight 140–160 g) and prepared using the method of Pogo et al. (16) as described in a previous paper (14). Cytosol (105,000*g* supernatant) from rat liver was prepared and dialyzed overnight against distilled water (14). Protein content was estimated according to the method of Lowry et al. (17).

RNA Synthesis

Nuclei were incubated in a shaking water bath at 30°C. The total volume per tube was 0.5 ml, containing about 12 × 10^7 nuclei, together with 50 mM Tris–HCL (pH 7.5), 2.5 mM $MgCl_2$, 2.0 mM dithiothreitol, 0.5 mM $CaCl_2$, 0.3 mM $MnCl_2$, 5.0 mM NaCl, 2.5 mM Na_2HPO4, 5.0 mM spermidine, 2.5 mM ATP, 2.5 mM phosphoenolpyruvate, 0.5 mg/ml yeast RNA, 17.5 units pyruvate kinase, dialyzed cytosol from untreated animals (7 mg protein/ml), 1 mM CTP, 1 mM GTP, 0.4 mM UTP, 25 μl [^{14}C]UTP (57 mCi/mmole). In half of the experiments the incubation medium contained 1 μg/ml α-amanitin. At various times of incubation aliquots of 0.05 ml were taken, precipitated with 2 ml of 10% TCA on Millipore filters and washed (five times) with 3 ml of 5% TCA. [^{14}C] activity of the filters was measured in a Berthold 10 Channel Low-Level Counter. As illustrated by Figure 1, the UTP-incorporation into RNA linearly depends on the number of cell nuclei. Because not each preparation contained exactly the same number of cell nuclei, the linear regression for identical investigations was calculated by means of a computer program and the UTP incorporation was related to 12 × 10^6 cell nuclei. The respective regression coefficients (slope) were compared with a one-tailed Student's *t*-test with the control to determine if the slope of the control regression line was less than that of the treated group. A *P* value of <0.05 was accepted as statistically significant.

The chemicals used were purchased from E. Merck, Darmstadt, α-amanitin and nonlabeled nucleoside triphosphates from Boehringer, Mannheim, and [^{14}C]UTP from Amersham-Buchler, Braunschweig.

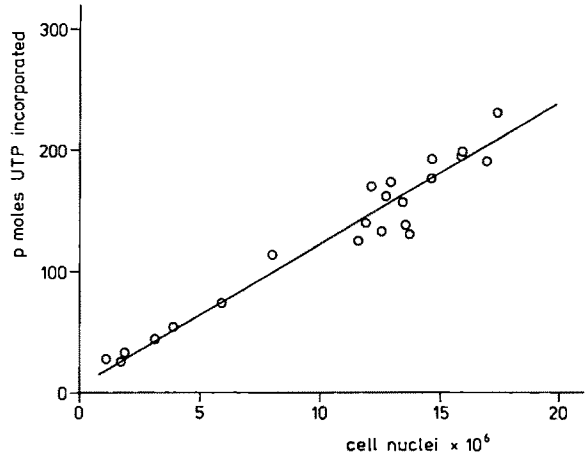

Figure 1. Dependence of UTP incorporation into RNA on the concentration of rat liver nuclei. Isolated nuclei from untreated animals were incubated in normal rat liver cytosol for 10 minutes. Linear regression analysis: y = b x + a; b = 11.53, Sb = 0.6066 (standard deviation of the slope); a = 7.62; r = 0.97; *n* = 22; sy.x = 16.1 (standard error of estimate).

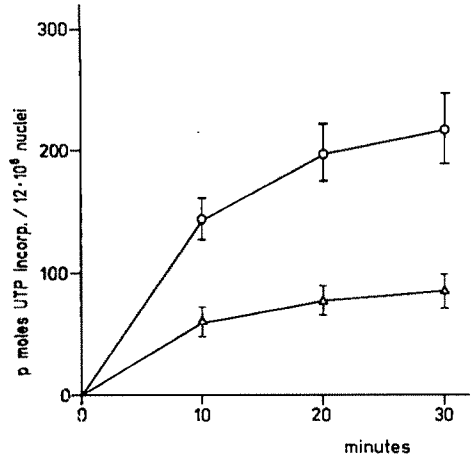

Figure 2. Incorporation kinetics of isolated nuclei from untreated animals (O) with normal rat liver cytosol, (Δ) with normal rat liver cytosol + α-amanitin (1 μg/ml). Values are given ± sy.x.

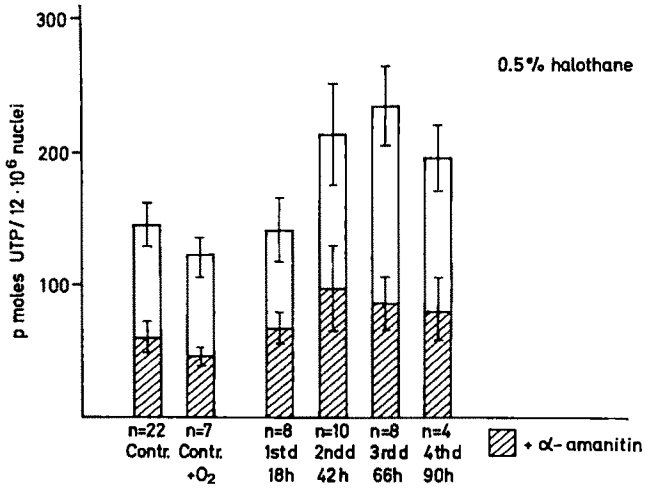

Figure 3. UTP incorporation into RNA of isolated cell nuclei after administration of 0.5% halothane. Incubation time: 10 minutes. Values are given ± sy.x. Linear regression analysis: Control: see Figure 1. Control + oxygen: b = 9.352; Sb = 0.8728; a = 9.672; r = 0.979; sy.x = 15.14. Second day: b = 15.199; Sb = 3.66; a = 29.805; r = 0.916; sy.x = 38.386. Third day: b = 15.772; Sb = 1.844; a = 43.887; r = 0.955; sy.x = 30.87. Fourth day: b = 15.332; Sb = 8.111; a = 10.977; r = 0.981; sy.x = 25.649.

Results

The transcription system described earlier was used to investigate the effect of in vivo inhaled volatile anesthetics on in vitro transcription. Typical incorporation kinetics of UTP into RNA by cell nuclei derived from control rats are illustrated in Figure 2. Apparently RNA polymerase I as well as RNA polymerase II are involved in the in vitro transcription, because addition of α-amanitin (1 μg/ml), which inhibits the polymerase II (18), to the incubation medium caused a 60% inhibition of RNA synthesis.

After the inhalation of 0.5% halothane in oxygen for 18 hours, an increase takes place in the transcription rate as compared to the incorporation by cell nuclei from control rats. Figure 3 demonstrates this stimulatory effect on RNA synthesis after 10 minutes of incubation. Additionally, a moderate reduction in transcription is observed in cell nuclei from rats kept in oxygen for 18 hours, although compared to the control with a two-tailed *t*-test, it would not be accepted as significant ($P = 0.06$). The increase in UTP incorporation after exposure to volatile anesthetics involves the products of RNA polymerase I as well as those of RNA polymerase II, reaching a significant maximum of 60% on the third day, significantly different from control data ($P = 0.005$). During the subsequent days the increase in the transcription rate gradually decreased.

Enflurane 1% (Fig. 4) also resulted in a 35% increase in in vitro RNA synthesis on the second day after treatment. Although this change was not statistically significantly different from untreated rats, the increase is, when compared with the results after inhalation of 100% oxygen, statistically significant ($P = 0.04$).

Figure 5 shows that 0.7% isoflurane was associated immediately after cessation of exposure to the anesthetic with a significant 42% increase in transcription compared with untreated rats ($P = 0.0025$), an effect that disappeared by the fourth day.

In vitro RNA synthesis of isolated cell nuclei derived from phenobarbital-treated rats is shown in Figure 6. In vitro transcription increased on the third day after the beginning of oral administration, reaching a significant maximum on the fifth day ($P = 0.005$) and disappeared by the second day after phenobarbital administration had stopped (9 days since initiation of phenobarbital pretreatment).

Discussion

The present results demonstrate that the three volatile anesthetics studied lead to a stimulation of in vitro transcription in rats. The difference in times until the increase in transcription reached a maximum seems to be inversely related to the rate of biotransformation of the anesthetics. In humans, 17–20% (19) of inhaled halothane, 2.4% of enflurane (20), and ≤0.2% of isoflurane is metabolized (21). Even though in the rat slightly different rates may be expected, there should be no major difference. Therefore, isoflurane, which is scarcely metabolized, seems to have the same effect on the RNA synthesis immediately after cessation of the inhalation as halothane after 3 days. It is conceivable that the unchanged

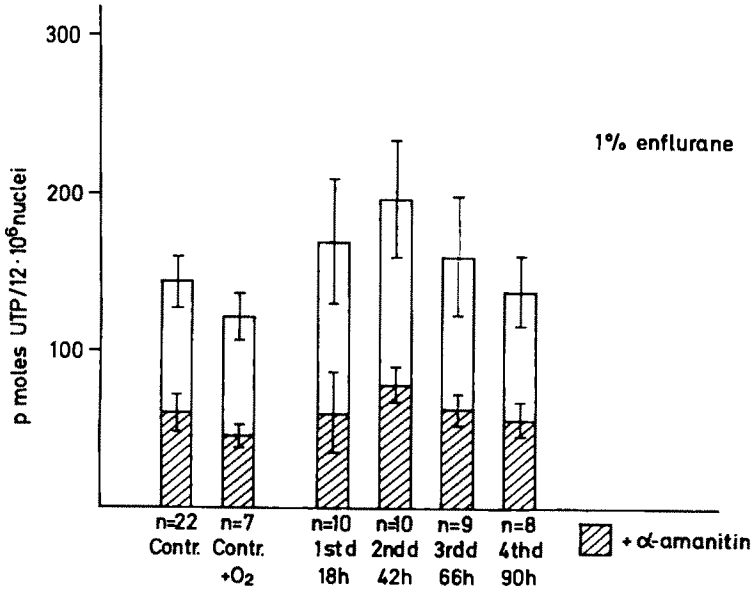

Figure 4. UTP incorporation of isolated cell nuclei after administration of 1% enflurane. Incubation time: 10 minutes. Values ± sy.x. Linear regression analysis: First day: b = 12.182; Sb = 2.436; a = 22.80; r = 0.87; sy.x = 39.80. Second day: b = 14.882, Sb = 2.639; a = 16.912; r = 0.894; sy.x = 37.98. Third day: b = 12.912; Sb = 2.445; a = 4.915; r = 0.894; sy.x = 38.285. Fourth day: b = 10.862; Sb = 1.263; a = 7.346; r = 0.962; sy.x = 23.017.

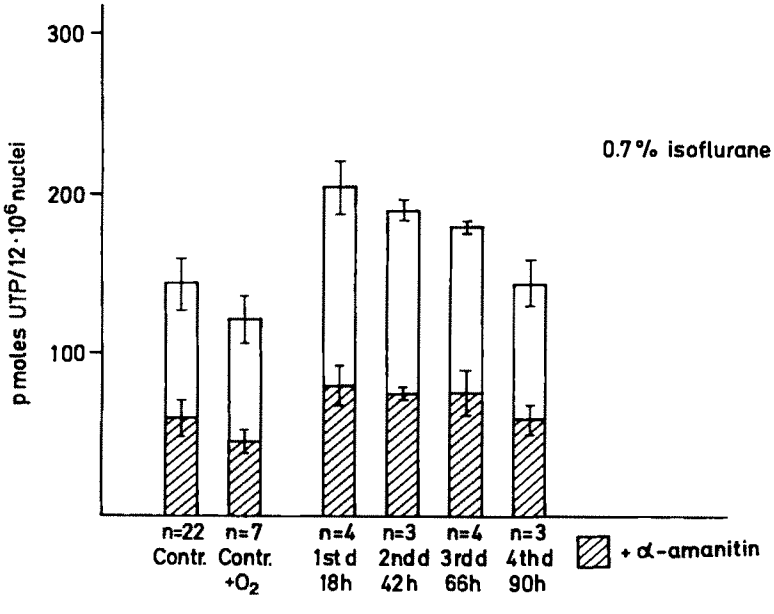

Figure 5. UTP incorporation of isolated cell nuclei after administration of 0.7% isoflurane. Incubation time: 10 minutes. Values ± sy.x. Linear regression analysis: First day: b = 17.1082; Sb = 1.489; a = 0.443; r = 0.988; sy.x = 15.52. Second day: b = 15.782; Sb = 0.609; a = 2.161; r = 0.998; sy.x = 6.681. Third day: b = 15.032; Sb = 0.328; a = −0.117; r = 0.999; sy.x = 4.132. Fourth day: b = 11.726; Sb = 1.161; a = 4.444; r = 0.990; sy.x = 15.432.

isoflurane has the same potential effect on transcription as the metabolites of halothane.

The nature of the additionally transcribed RNA is uncertain. The above results agree with studies on phenobarbital. During oral administration of phenobarbital an increase in in vitro RNA synthesis was observed on the third day, reached a maximum on the fifth day and disappeared 2 days after cessation of drug administration. Phenobarbital is the classic substance to induce cytochrome P-450 (22,23). Several authors found an increase in m-RNA for the apoprotein of cytochrome P-450 after phenobarbital administration (24–27). Moreover, there are indications that enzyme induction takes place on the transcription level (28,29). That the increase in RNA synthesis by volatile anesthetics may be related to enzyme induction could be concluded from the paper of Brown and Sagalyn (30), who studied diethyl ether and methoxyflurane: with diethyl ether an increase in cytochrome P-450 as well as an increase in the turnover rate of several drugs was observed, but this did not occur with methoxyflurane. Plummer et al. (31) found a slight increase in hepatic microsomal cytochrome P-450 content after chronic exposure of male rats to halothane, whereas in the case of enflurane and isoflurane this effect was not observed. Rietbrock et al. (32) reported that, in female rats, repeated anesthesia with halothane did not affect hepatic cytochrome P-450 content 3 days after the last exposure, but markedly reduced hexobarbital sleeping time.

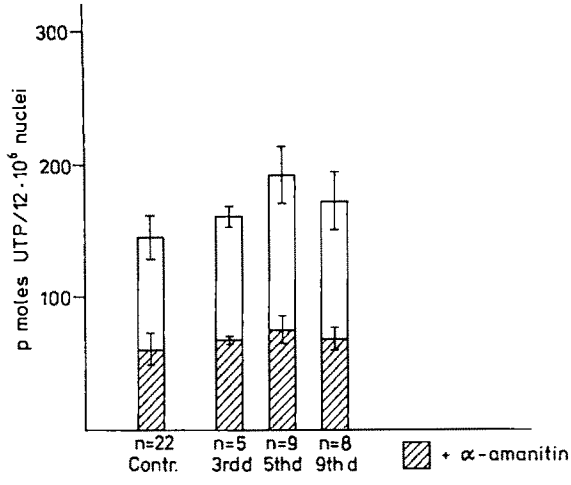

Figure 6. UTP incorporation of isolated cell nuclei after administration of phenobarbital in the drinking water for 7 days. Incubation time: 10 minutes. Values ± sy.x. Linear regression analysis: Third day: b = 13.249; Sb = 0.664; a = 0.978; r = 0.995; sy.x = 8.125. Fifth day: b = 16.213; Sb = 1.739; a = −3.426; r = 0.957; sy.x = 22.92. Ninth day: b = 14.413; Sb = 1.623; a = 1.225; r = 0.958; sy.x = 22.155.

Other authors even found a decrease in the amount of hepatic cytochrome P-450 (33,34).

The reason for these contradictory results may be different experimental conditions, including sex of the rats, O_2 concentration, dosage of the anesthetics, and chronological arrangement of the measurements. That the anesthetics indeed have a direct or indirect effect on the genome and not on other mechanisms such as the uptake of precursors into the cell is shown by the fact that the isolated cell nuclei increasingly transcribe RNA in vitro in the presence of cytosol from untreated animals. The information for an increase in transcription therefore has to be located in the nucleus. Cytosol from animals exposed to the anesthetics under the above-mentioned conditions did not show a stimulatory effect on isolated cell nuclei from untreated animals (data not shown). Further investigations are needed to determine whether the augmented transcription rate caused by volatile anesthetics analogous to that seen with phenobarbital concerns mainly the m-RNA for cytochrome P-450, whether the additionally transcribed genes are identical with those which can be induced by phenobarbital, or whether they are coding for isoenzymes.

Although a correlation of the effect of the three examined volatile anesthetics on the transcription activity of isolated cell nuclei and a possible hepatic injury by now cannot be deduced from the above results, it should be concerned that transcription is one of the fundamental cellular functions and interference with it may lead to severe consequences for cellular viability. Isoflurane, which is only slightly metabolized, also leads to a marked stimulation in the transcription rate immediately after cessation of inhalation. Thus, the possibility exists that there might be a direct effect of the unchanged anesthetic on the regulation of transcriptional processes.

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Effect of Adding Sodium Bicarbonate to Bupivacaine for Spinal Anesthesia in Elderly Patients

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RACLE JP, JOURDREN L, BENKHADRA A, POY JY, FOCKENIER F. Effect of adding sodium bicarbonate to bupivacaine for spinal anesthesia in elderly patients. Anesth Analg 1988;67:570–3.

The effect of added sodium bicarbonate on plain bupivacaine spinal anesthesia is unknown. Forty patients aged 75 years or older, ASA II or III, undergoing orthopedic lower limb surgery under spinal anesthesia were randomly classified into two groups. Just before injection, either 0.2 ml normal saline (group I) or 0.2 ml 0.42% $NaHCO_3$ solution (group II) was added to 20 ml 0.5% bupivacaine hydrochloride. All patients then received intrathecally 3 ml (14.85 mg) of the bupivacaine solution in the lateral decubitus position. The segmental level of sensory loss was tested using forceps. The median time required to achieve maximal height of the sensory blockade and the median highest level of sensory anesthesia did not differ in the two groups. Alkalinized bupivacaine increased significantly the median times for regression to the T12 and L2 segments by 15 and 25 minutes, and the duration of complete motor block by 15 minutes, as compared to the hydrochloride salt. The clinical importance of such modest prolongations seems limited.

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHETIC TECHNIQUES—spinal.

The pH of the commercial 0.5% bupivacaine solution is acidic (1). Increasing the pH of this solution could enhance the fraction of bupivacaine present in its nonionized form, resulting in vitro in a more rapid onset time of conduction block (2,3).

The initial studies of Bromage et al. (4,5) reported in humans a more rapid onset and increased intensity of motor and sensory blockade during extradural anesthesia with carbonated solutions of lidocaine compared with the use of lidocaine hydrochloride solutions. However, double-blind studies in which lidocaine carbonate was compared with lidocaine hydrochloride for extradural blockade have failed to demonstrate significantly more rapid onset of action (6,7). Time to onset of action was also the same when bupivacaine carbonate was compared with bupivacaine hydrochloride (8).

It has been reported that the addition of sodium bicarbonate to bupivacaine solution immediately before injection reduces the latency of brachial plexus anesthesia (9), but this has recently been questioned (10). No study has been reported on the effects of alkalinization of plain bupivacaine for spinal anesthesia. Thus, the present study was undertaken to assess the effect of adding sodium bicarbonate to 0.5% plain bupivacaine solution for spinal anesthesia in elderly patients.

Methods

Forty patients over the age of 75 years scheduled for orthopedic lower limb surgery under spinal anesthesia were studied. All were in ASA categories II–III. All patients gave informed oral consent after receiving a detailed explanation of the procedure and received a spinal anesthesia in the lateral decubitus position as described elsewhere (11). The patients were randomly allocated to two groups according to the permutation table of Cochran and Cox. A volume of 0.2 ml 0.9% sodium chloride was added to 20 ml 0.5% bupivacaine plain solution, and patients in group I received intrathecally 3 ml (14.85 mg) of this 0.495% bupivacaine solution (pH 5.38 ± 0.05 [1]). A volume of 0.2 ml 0.42% sodium bicarbonate was also added to 20 ml 0.5% bupivacaine plain solution, and patients in group II received intrathecally 3 ml (14.85

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mg) of this 0.495% alkalinized bupivacaine solution (pH 6.87 ± 0.01 [1]). The volumes were measured using a 1-ml insulin syringe. The normal saline and sodium bicarbonate were added and mixed thourouly at the time of injection.

The time of completion of injection of the local anesthetic solution into the subarachnoid space was used as the basis for measurement of all time intervals. Dermatomal levels of sensory anesthesia were measured bilaterally at the midclavicular line, in the perineum, and on the legs by pinching with a Pean forceps at 2-minute intervals for 30 minutes. A dermatomal chart was used for each patient to ensure accurate assessment of anesthetic level. Sensory anesthesia was considered complete when the patient did not respond to forceps closed to its first rachet (12). When levels of anesthesia were not equal bilaterally, the higher was used for statistical purposes. Motor blockade was assessed at the same time as sensory levels and tested using criteria described by Bromage (4): 0, no impairment of movement of legs and feet; 1, barely able to flex knees, no impairment of movement of feet; 2, unable to flex knees, barely able to move feet ; 3, unable to move feet or knees. Thereafter, anesthesia and motor blockade were assessed every 15 minutes until anesthesia had regressed to the L4 level and motor blockade had regressed to degree 0. The mean times to two- and four-segment regression of the level of anesthesia from its highest level, and the time to regression to T12 and L2 segments were recorded. Test procedures were performed by two trained anesthetic nurses who were unaware of the nature of the study and not present at the time of injection.

Blood pressure and heart rate (sphygmomanometer) were measured at 2.5-min intervals throughout anesthesia and surgery and at 15-minute intervals during recovery. If during establishment of spinal blockade systolic blood pressure (SBP) decreased more than 20% below levels observed under resting conditions despite preloading with 500 ml Ringer's lactate solutions, the rate of IV fluids was increased. If that was not sufficient (SBP < 20% but > 30% above baseline levels for 10 minutes or more), or if hypotension occurred (SBP < 30% [13]), then IV ephedrine (15–30 mg) was given. Resting blood pressure was determined during the anesthesiologist's preoperative visit the day before surgery (14). When the clinical condition permitted, and with the return of active lower limb movements, the patients were returned to the surgical ward where they were kept supine for 12 hours.

All data are presented as means ±SD, together with medians and ranges. Statistical analysis was performed using Wilcoxon rank-sum test for all data. A value of $P < 0.05$ was considered statistically significant.

Table 1. Sensory Levels after Intrathecal Administration of Bupivacaine with or without Sodium Bicarbonate (Mean ± SD)

	Group I Plain	Group II Alkalinized
Highest level of anesthesia		
Median	T10	T10
Range	T12–T4	T12–T6
Time from injection to highest level (minutes)		
Mean	9.1 ± 5.3	10.3 ± 5.5
Range	2–20	2–26
Time for two-segment regression (minutes)		
Mean	110 ± 43	120 ± 44
Range	60–210	50–180
Time for four-segment regression (minutes)		
Mean	165 ± 35	190 ± 69
Range	120–240	60–330
Time for regression to T12 (minutes)		
Mean	109 ± 47	133 ± 44*
Range	50–210	50–240
Time for regression to L2 (minutes)		
Mean	157 ± 37	197 ± 54†
Range	90–225	120–330

*Significant differences by Wilcoxon rank-sum test: $P < 0.01$.
†Significant differences by Wilcoxon rank-sum test: $P < 0.05$.

Results

No significant differences existed between the two groups with regard to age, weight, or height. Median highest levels of anesthesia were similar (T10) in the two groups (Table 1). Ranges (18 and 24 minutes) in time for achievement of the highest level of sensory anesthesia were so great that the mean times to onset of sensory blockade did not differ significantly in the two groups. The median time for regression of the level of sensory anesthesia by the two segments were identical (120 minutes). There were also no significant differences in median time for four-segment regression (175 vs 190 minutes). Compared with plain bupivacaine group, the median time for regression of the level of sensory anesthesia to T12 was significantly longer in group II (105 minutes: +15 minutes, +14%) than in group I (120 minutes). Median time to regression to L2 was also significantly longer (180 minutes: +25 minutes, +16%) with bupivacaine plus sodium bicarbonate solution than that with bupivacaine plain solution (155 minutes).

Table 2. Characteristics of Spinal Motor Block in the Two Groups

	Group I Plain	Group II Alkalinized
Time to onset of total motor block (minutes)		
Mean ±SD	7.5 ± 4.2	7.0 ± 4.8
Range	2–20	2–20
Duration of grade 3 motor block (minutes)		
Median	165	180*
Range	60–210	120–330
Duration of grade 2 motor block (minutes)		
Median	180	210*
Range	90–240	150–350
Duration of grade 1 motor block (minutes)		
Median	210	250†
Range	120–270	180–370

*Significant differences by Wilcoxon rank-sum test: $P < 0.05$.
†Significant differences by Wilcoxon rank-sum test: $P < 0.02$.

Table 3. Systolic Blood Pressure (SBP) and IV Fluid Administration during the First 30 minutes (Mean ±SD)

	Group I	Group II
Resting SBP (mm Hg)		
Mean	147 ± 22	155 ± 23
Range	115–190	110–190
Lowest level of SBP (mm Hg)		
Mean	122 ± 25	123 ± 22
Range	70–170	90–160
Mean percentage of resting values	−17 ± 11	−20 ± 10
Volume of lactated Ringer's solution given (ml/kg)		
Mean	11.8 ± 5.2	10.4 ± 2.8
Range	6.1–20	6.1–17.4

All patients had complete motor blockade (grade 3) of the lower limbs. The time to onset of total motor block did not differ significantly between the two groups (median value 6 minutes, Table 2). Significant differences in median duration of grade 3 motor block were found between groups I and II (+15 minutes, +9%). The median duration of grade 2 and grade 1 motor blockade was also significantly longer with administration of alkalinized bupivacaine (+30 minutes).

Resting blood pressure did not differ significantly between the two groups (Table 3). The decrease in SBP below resting values was not significantly greater in group II than it was in group I. Four patients in group I and five in group II received ephedrine either because of hypotension (two and four patients, respectively) or a decrease in SBP (<20% but >30%) for 10 minutes or more. No statistically significant difference was noticed among the groups in the amount of intravenous fluids given during the first 30 minutes. Anesthesia was considered satisfactory in all cases because no supplementation with intravenous or inhalation anesthesia was required for pain during surgery.

Discussion

Plain bupivacaine was chosen because this local anesthetic permitted an effective satisfactory spinal anesthesia for patients undergoing lower extremity surgery of medium duration. Previous studies had suggested 15 mg plain bupivacaine as a suitable dosage to obtain a maximum level of anesthesia at T10 (10). Volume and concentration of sodium bicarbonate solution chosen in the present study (0.2 ml 0.42% $NaHCO_3$) were different from that of Hilgier (9) (0.1 ml 0.84% $NaHCO_3$) and that of Desparmet et al. (15) (0.6 ml 0.14% $NaHCO_3$) because a volume of 0.1 ml seemed too low to be used with precision, and a volume of 0.6 ml seemed too high.

The present study showed that the onset of plain bupivacaine spinal anesthesia was not modified despite, according to Bonhomme et al. (1), an increased in pH from 5.38 to 6.87. It must be emphasized that this study was concerned with bupivacaine spinal anesthesia only and that different results might be obtained at other sites of injection or with other local anesthetic agents. It is also possible that a commercialy prepared carbonated bupivacaine solution might behave differently. Previous studies in vitro by Catchlove (16) demonstrated that addition of carbon dioxide shortened the time of onset and increased intensity of the conduction block produced by bupivacaine. However, in vivo carbonated bupivacaine failed to shorten time of onset of extradural analgesia (8). It was suggested that carbonated solutions were rapidly buffered in vivo so that it was proposed to add sodium bicarbonate to the local anesthetic at the time of injection (2,9). Despite this, in the present study, onset of bupivacaine spinal anesthesia was not shortened. The discrepancy between in vitro and in vivo studies might in part be explained in two ways. First, cerebrospinal fluid probably has a relatively limited buffering capacity: after subarachnoid 3 ml 0.5% bupivacaine hydrochloride (pH 6.00 ± 0.2), the decrease in CSF pH is only 0.08 (17,18). Second, because precipitation occurs if more than 0.1 mEq $NaHCO_3$ is added to 20 ml 0.5% plain bupivacaine, the maximal increase in pH can only be 1.49 units. This is quite different than with lidocaine: 2 mEq $NaHCO_3$ added to 20 ml 1.5% lidocaine results in a solution pH increase of 2.40 (19).

In this study, the maximal levels of sensory anesthesia in patients given pH-adjusted local anesthetic solution intrathecally were no different from the levels achieved in patients given plain solution. This agrees with studies on the effects of carbonated bupivacaine (8) and alkalinized lidocaine (19) on extradural anesthesia.

The present study also indicates that added sodium bicarbonate appears to produce no prolongation of two- and four-segment regression time of higher level of plain bupivacaine spinal anesthesia, but significantly prolongs the time for regression to T12 and L2 by an average of 15 and 25 minutes. It is possible that such a modest prolongation is clinically inconsequential. For extradural anesthesia, Brown et al. (8), using carbonated bupivacaine, found no prolongation of sensory blockade, while McMorland et al. (20), using alkalinized bupivacaine in term parturients, found a statistically significant increase in duration of sensory analgesia, but only by 17 minutes. It is not known whether added $NaHCO_3$ can prolong regional blocks. The common view is that alkalinized solutions can produce a greater amount of free local anesthetic base to be absorbed by the nerve fibers (2,21,22). Thus, one can postulate that added sodium bicarbonate to plain bupivacaine for spinal anesthesia increases the amount of free bupivacaine base to be absorbed by the spinal nerve roots, especially those around the site of injection.

No difference in maximum decreases in SBP below resting levels was encountered in the two groups in the present study. This was probably because there were differences in latency or levels of spinal anesthesia with alkalinized bupivacaine compared with the hydrochloride salt. With extradural anesthesia, alkalinized lidocaine is associated with significantly greater magnitude and rate of decline in SBP compared with hydrochloride lidocaine (23).

In conclusion, alkalinization of plain bupivacaine for spinal anesthesia in elderly patients produces a statistically significant but clinically inconsequential prolongation of sensory and motor blockade in terms of total duration in lower thoracic and lumbar segments.

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SPECIAL ARTICLE

Alas, Poor Trendelenburg and His Position!

A Critique of Its Uses and Effectiveness

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History

In the 1860s, Friedrich Trendelenburg (1844–1924), a German urologic surgeon, popularized the high pelvic posture that still bears his name. In World War I, the "Trendelenburg position" was advocated in the treatment of shock. Since then, modifications of the original posture have been used in diverse situations, with applications found for "high," "low," and "reverse-Trendelenburg." Over the past 50 years, laboratory and clinical studies have described the physiologic effects of the Trendelenburg position in normal and hypotensive states. Because of conflicting results, opinions abound with regard to usefulness of the position in hypovolemic or septic shock, for patients under general or regional anesthesia, and in patients with spontaneous or controlled ventilation. Medical dictionaries hardly agree on the details of the Trendelenburg posture (1–6), and the "Trendelenburg" of today, merely the head down position, bears slight resemblance to that described over a century ago.

Friedrich Trendelenburg neither originated the position nor first described it. He found the supine, elevated pelvic position particularly useful in providing operative visualization for surgical repair of vesicovaginal fistulas. This position had already been described by Bardenhauer of Cologne but was extensively used and taught by Trendelenburg after 1860 (7).

In 1873, Esmarch further elucidated the high pelvic posture in his text, Surgical Technique, under the heading Suprapubic Cystotomy. "For this operation, Trendelenburg's position is generally employed. By raising the trunk and legs of the patient, his body is placed in an oblique position of 45°" (7). In 1885, Willy Meyer of New York published a paper concerning the high pelvic posture and ascribed it to his surgical instructor in the Bonn Clinic, F. Trendelenburg (8–11). Trendelenburg himself depicted the posture for the first time in 1890. "If one places the body of a patient on the operating table in such a way that the symphysis pubis forms the highest point of the trunk and the long axis of the trunk forms an angle of at least 45° with the horizontal, then the various organs . . . fall into the concavity of the diaphragm by virtue of their weight" (12). The 1892 edition of Keen and White's Surgery described the high pelvic position, but credited Bardenhauer as the first to use it to surgical advantage (7). Nevertheless, the eponym thenceforth associated with the position was Trendelenburg, prompted both by the references cited and an illustration in Fenwick's Urinary Surgery, 1894 (8,13).

As shown in Fenwick's text, the high pelvic posture was first achieved by dangling the patient's legs over the shoulders of an attendant while the surgeon operated (8,10) (Fig. 1). The weight of the legs rotated the pelvis toward a horizontal but elevated position (11). By the 1920s, a table attachment for producing the head-down, knee-flexed position was available, with the additional support of padded shoulder rests, as illustrated in the then current practical surgery texts edited by Bickham (1924) and Juilly (1928) (8).

Metamorphosis

Today Trendelenburg has lost its identity. The International Dictionary of Medicine and Biology de-

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Pelvic elevation for urologic surgery (Meyer, 1885).

Figure 1. Pelvic elevation for urologic surgery: the Trendelenburg position according to Meyer. (Reproduced from Meyer W. Ueber die Nachbehandlung des hohen Steinschnittes sowie über Verwendbarkeit desselben zur operation von Blasenscheidenfisteln. Arch Klin Chir 1885:31:49.)

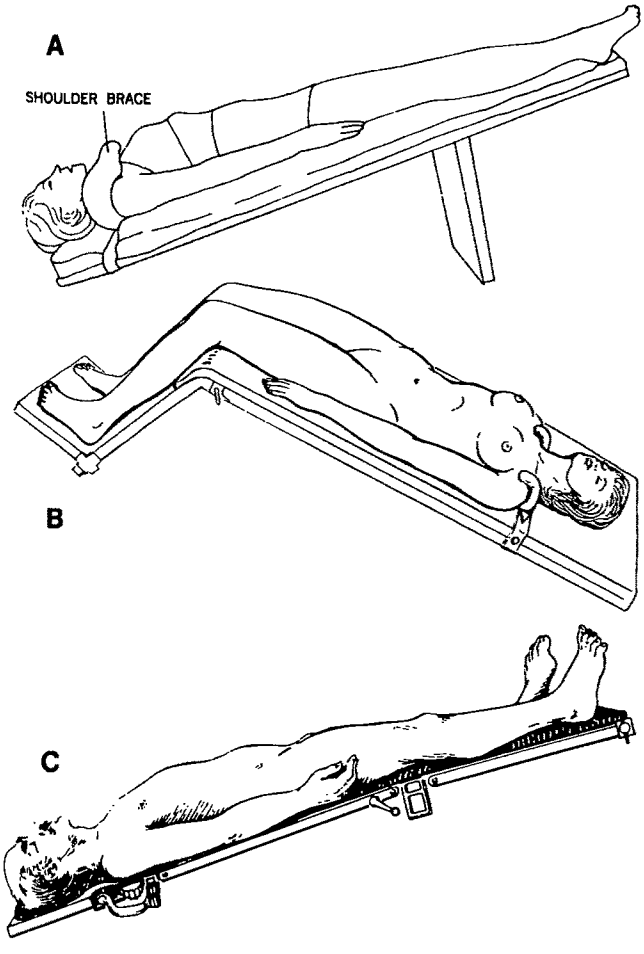

Figure 2. The Trendelenburg position according to several lexicographers. **(A)**, Taber's Cyclopedic Medical Dictionary (4); **(B)**, Dorland's Illustrated Medical Dictionary (3); **(C)**, Stedman's Medical Dictionary (2). Reprinted with permission of the publishers: FA Davis, WB Saunders, and Williams & Wilkins, respectively.

scribes the Trendelenburg position accurately, except for the requisite 45° tilt. "A position in which the subject lies supine—with the knees higher than the rest of the body, hanging over the edge of a supporting surface and forming the apex of a right angle so that the body forms an inverted V with the pelvis elevated above the head. Also called high pelvic position" (1). A similar definition is given in several dictionaries, Dorland's (3) and Butterworth's (6). Stedman's (2), Taber's (4), and Blakiston-Gould's (5) describe the posture only as supine, with head tilted downward, reflecting popular usage of the term (Fig. 2).

Taber's also states, "this (Trendelenburg) position is used in abdominal surgery, in case of shock, or low blood pressure" (4). Presently, variations are also used in pelvic surgery, to improve cerebral blood flow, to treat venous air embolism, to engorge cervical vessels for central venous catheter placement, to prevent aspiration at onset of vomiting, to correct pulmonary ventilation/perfusion mismatch, and to achieve a high level of spinal or epidural anesthesia. Many of these applications are controversial, because all present risks as well as benefits.

Circulatory Effects

It is essential to distinguish between a moderate and extreme head-down position. As generally taught, "postures with the head lowered are more favorable to the circulation; with the head raised, more favorable to the respiration" (7). Indeed, a recent study suggests that normotensive, normovolemic patients with nocturnal angina are less symptomatic in reverse Trendelenburg position (14) or a cardiac chair (15). However, the augmented cardiovascular stress to patients with coronary artery disease (CAD) of a head-down position versus horizontal was quantified in a study of patients scheduled for coronary artery bypass surgery (16). Although heart rate (HR) was unaltered with position change, presumably because these patients were receiving some form of β-adrenegic or calcium channel blocker therapy, acute elevations occurred in central venous pressure (CVP), mean and systolic arterial pressures (MAP, SAP),

pulmonary capillary wedge pressure (PCWP), and mean pulmonary artery pressure (MPAP), suggestive of acute volume loading. The rate–pressure product (RPP = HR × SBP) was elevated in all patients, implying increased myocardial oxygen demand. Central blood volume and pressure changes were most marked in those patients with compromised ejection fractions (<54%), where an increase in myocardial oxygen demand is least well tolerated and subendocardial ischemia most likely to occur (16).

Although endogenous volume loading of the central circulation was implied in this and other studies, a 1985 noninvasive study of healthy, normovolemic subjects placed in 15° head-down position showed only a 1.8% (median) central displacement of blood volume. This small volume shift was not enough to cause significant hemodynamic changes (17). In normotensive subjects, the baroreceptor reflex may be responsible for the stable cardiovascular status, because the head-down position in normovolemic humans has been shown to increase CVP and cardiac output (CO) without increasing HR or systemic vascular resistance (SVR) (18). The carotid and aortic baroreceptors normally respond reflexly to an increase in hydrostatic pressure with systemic vasodilation and bradycardia (19).

A study on patients with acute cardiac disease or sepsis, both normal and hypotensive, failed to document any beneficial hemodynamic effect of 30° head-down positioning (19). As in the study of patients with CAD, CVP, PCWP, and MPAP were significantly increased with head-down positioning of normotensive, cardiac patients. A slight increase was noted in MAP and RPP, whereas SVR and cardiac index (CI) decreased. Interestingly, in 7 of 61 (11%) normotensive patients, the head-down position was associated with a decrease in MAP of more than 10 mm Hg owing to systemic vasodilation without compensatory increase in CO; in 10 of 61 (16%), MAP increased ≥10 mm Hg owing to an elevation in SVR (MAP–CVP). The septic, normotensive group showed the expected initial high flow (CO) and low SVR. Head-down positioning caused an increase in PCWP and MPAP, but not CVP.

Notably, as with normotensive patients, in hypotensive (shock) patients (50% cardiac, 50% septic) there was no significant effect on MAP of head-down tilt. Unlike normotensive patients, these patients did not register higher left heart filling pressures (PCWP), and CO decreased, whereas SVR increased (19). This study, therefore, failed to show any benefit of the head-down posture for normotensive or hypotensive patients.

Another study yielded similar results in hypotensive, peripherally vasodilated patients (20). Systolic, diastolic, and mean arterial pressure decreased significantly in most of these patients when position was changed from horizontal to 10° head-down; there was no consistent change in HR. On the average, CI was not changed significantly by positioning but ranged from +52 to −14% change, in inverse relation to measured plasma volume. Five normotensive controls similarly monitored in 10° tilt had no consistent change in MAP or CI. The authors concluded that the head-down position should be abandoned in the routine treatment of protracted hypotension.

A more recent study concerning 13 normotensive patients in the 10° head-down position found a small but significant (10%) increase in CI without elevation of CVP, PCWP, HR, or SVR. Although this investigation suggests a potential benefit from this position for hypovolemic patients based on normal subject data, the authors stated "only a prospective, randomized trial of Trendelenburg in trauma victims will adequately determine the efficacy of this therapy" (21).

Thus, despite widespread use of the head-down position to treat the acutely hypotensive patient, there are no well-documented, predictable hemodynamic or clinical benefits derived from this maneuver. Many clinicians now believe that the head-down position is contraindicated in the treatment of shock and prefer instead to elevate only the patient's legs, thus providing autotransfusion without potentially harmful baroreceptor reflex changes or cerebral congestion related to dependent positioning (8).

Jugular venous distention induced by the head-down position is commonly used for placement of central venous catheters. However, this is not always a benign maneuver. Venous pressure is increased as much as four times normal and may affect cerebral circulation, although normal patients accommodate with elevations in MAP and cerebral spinal fluid (CSF) pressures and do not experience appreciable changes in cerebral blood flow (CBF) until mean blood pressure falls below 50 mm Hg. As noted above, the baroreceptor reflex results in a decline in mean arterial blood pressure and carotid arterial blood pressure (CABP) inversely proportional to the transient increase in cerebral perfusion pressure during head-dependent positioning. In the anesthetized dog, a 30° head-down tilt decreased CABP and CBF. In precarious circumstances, an increase in CSF pressure could impair cerebral circulation, especially if venous dilation were compounded by inadequate pulmonary ventilation or, conversely, by hyperventilation, which diminishes cerebral blood flow. Acute glaucoma can be worsened with the additionally

elevated intraocular venous pressure. The effect of position on intracranial pressure must be carefully observed in patients with head trauma or cerebral tumor. Finally, if the head-down position is maintained while fluid resuscitation is overambitious, edema of the head and neck usually occurs.

While intravascular pressures increase in the upper torso, pelvic and abdominal structures are subject to decreased transmural vascular pressures, thus diminishing surgical blood loss in these areas. This is not without penalty, for the lesser venous pressures may increase the risk of air embolism. As little as a 10° head-down tilt has been associated with massive air embolism during abdominal hysterectomy (22).

Injury to the Legs

The legs are not immune to circulatory dysfunction in the true Trendelenburg position; thus they must be freely supported and not tightly strapped, or venous thrombosis and pulmonary embolism might occur postoperatively. Pressure on the popliteal space resulting from table flexion, or at the ankles from straps, must be guarded against. Even with nonbinding supports, venous stasis probably occurs with the lower legs in flexion. One study comparing dye clearance in leg veins showed increased stasis if the legs were flexed just 15° below the horizontal, versus 15° above horizontal, in "lithotomy Trendelenburg" position. Clearance was three times more rapid with less knee flexion (23), that is, 50 versus 80° (assuming 20° head-down tilt and 45° hip flexion). The Trendelenburg 90° knee flexion might impede flow even more, although the lack of hip flexion would alter the fluid dynamics.

Brachial Injury

Likewise, the arms are not free of risk in the Trendelenburg position, not so much from venous stasis but because of possible nerve compression. Arm extension must not be so extensive (>90°) as to stretch the brachial plexus; shoulder braces must not impinge on the plexus. The more peripheral nerves, particularly radial and ulnar, must be protected by adequate padding on the armrest or by being placed against the body. Specifically, wrist or arm straps should not tightly bind the elbow or wrist areas.

An unusual neurologic complication of "reverse Trendelenburg" occurred in a patient placed in 20° head-up tilt to reduce bleeding during a nasal operation (12). The foot rest used to maintain the patient's position supported his weight against the balls of the feet. This led to an apparent convulsion, which was actually postural ankle clonus, after just 3 minutes of head-up position. Had the entire foot been supported, this complication would have been prevented.

Respiratory Changes

Studies assessing pulmonary function have not in general shown significant compromise resulting from head-down positioning itself. However, the potential for compromise exists. There may be a predilection to develop atelectasis if deep breaths are not intermittently supplied when mechanical ventilation is used. When left atrial pressure (PWCP) increases in relation to alveolar pressure, the tendency toward atelectasis, pulmonary congestion, and edema is enhanced. Increased airway pressure, as in PEEP of 5 cm H_2O, may minimize this complication. Studies of spontaneously breathing, normal volunteers in a 35° head-down position during light general anesthesia show no change in minute volume or pH, although the work of breathing is increased. At 45° head-down tilt in these patients decreased functional residual capacity (FRC), total lung volume (TLV), and pulmonary compliance have been demonstrated (8). There is also a diminution in physiologic deadspace and increased diffusion capacity. At 20° tilt, vital capacity is 86% that in the sitting position in these subjects. To be sure, the changes are more marked in obese, elderly, or debilitated patients and enhanced by placement of surgical packing and use of retractors in the upper abdomen.

These changes in lung volume do not result in major changes in gas exchange in young patients during spontaneous breathing. A compensatory increase in respiratory rate, and an occasional deep sigh, adequately maintain normal oxygenation and CO_2 levels. This was demonstrated in a study on 26 healthy patients anesthetized with epidural plus minimal general anesthesia by facemask. No changes in blood gases or minute volume (VE) were noted in these spontaneously ventilating patients, whether in a horizontal or 30° head-down position for a period of 1 hour (24).

Another potential complication is movement of the endotracheal tube (ETT). The ETT, firmly anchored at its proximal end, does not always move upward with the trachea as the diaphragm presses upward and displaces the lungs and carina. In this situation, the ETT can move from low in the trachea into the right mainstem bronchus, thereby resulting in underven-

tilation of the left lung (25). If the initial ETT placement is adjusted so the cuff is just below the cords, this potential for hypoxia and hypercapnea can be avoided.

The general belief is that head-down positioning can compromise pulmonary function, but this position may be therapeutic in some circumstances. For venous air embolism, Durant's maneuver (head-down and left lateral decubitus positioning) is used to prevent further progression to pulmonary embolism and consequent pulmonary and cardiovascular sequelae. Ventilation/perfusion mismatch can be corrected by this position as in the following case: an adult with bilateral, lower lung contusions and flail sternum dramatically recovered from life-threatening hypoxemia after 12 hours of 60° head-down positioning, whereas positive end-expiratory pressure (PEEP) had worsened the ventilation ($Paco_2$ increased to 70 mm Hg) without changing oxygenation. The improvement in gravity-dependent perfusion to the normal alveoli of the upper lobes resulted in a dramatic increase in arterial oxygenation (Pao_2) and decreased $Paco_2$ to normal (26).

Conclusion

With the passage of time, Trendelenburg's original posture has undergone metamorphosis. Although Trendelenburg's main intent was a surgical one, that is, to permit better operative visualization in a relatively bloodless field, subsequent variations, applications, and physiologic studies have demonstrated the potential for good and harm, so that the operator must be selective in its application.

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CLINICAL REPORTS

End-Tidal CO_2 Excretion Waveform and Error with Gas Sampling Line Leak

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Key Words: CARBON DIOXIDE—end-tidal. EQUIPMENT—end-tidal carbon dioxide analyzer. MEASUREMENT TECHNIQUES—end-tidal carbon dioxide. MONITORING—carbon dioxide tension. VENTILATION—breathing pattern.

We have previously observed during mechanical positive-pressure ventilation of anesthetized patients that when there is a loose connection between an end-tidal CO_2 sampling line and the CO_2 analyzer (Saracap), the CO_2 waveform is very unusual. The unusual waveform consists of a long duration plateau followed by a brief duration peak (Fig. 1, upper panel), rather than the normal almost square wave or rectangular CO_2 waveform (Fig. 1. lower panel), (1).

We hypothesized that the long plateau was caused by the entrainment of room air through the leaky connection by the continuous CO_2 analyzer suction. If this hypothesis is correct, then for any given true end-tidal CO_2 concentration, the height of the long CO_2 plateau should be a function of only the size of the leak (i.e., the quantity of room air entrained) and not the peak inspiratory pressure (PIP).

We also hypothesized that the brief peak at the end of the CO_2 excretion waveform occurs when the next PIP pushes end-tidal gas through the sampling line into the analyzer, with less entrainment of room air. The reason we cannot be certain that the next positive-pressure inspiration causes the brief peak is that there is a 3-second phase lag (delay) between the appearance of a CO_2 excretion waveform on the Saracap oscilloscope and the actual excretion of the CO_2. Thus, the effect of the next positive-pressure inspiration cannot be seen in real time and, therefore, the coincidence of the next inspiration and the brief CO_2 peak is uncertain. If our hypothesis is correct, then for any given true end-tidal CO_2 concentration, the height of the brief CO_2 peak should be a function of only the amount of PIP of the next breath, and not the size of the leak.

Finally, the O_2 and N_2O concentration values digitally displayed by the Saracap are mean exhalation values for the previous breath. As such, with a sample line/sample connection leak, the mean exhalation O_2 and N_2O concentration values should be determined by both the size of the leak and the PIP. The purpose of this Human Subjects Committee-approved study was to test these hypotheses.

Methods

We studied ten consenting ASA I or II patients; no patient had cardiac or pulmonary disease. After the induction of anesthesia and paralysis with standard techniques, and intubation of the trachea, each patient's respiratory rate (6–8 breaths/min), tidal volume (10–15 ml/kg), and PIP (20–30 cm H_2O) were adjusted to obtain normocapnia (end-tidal CO_2 tension [$P_{ET_{CO_2}}$] = 38±2 mm Hg). After the patients had stabilized with a constant $P_{ET_{CO2}}$ for more than 10 minutes, the surgical stimulus was constant, and there was no blood loss, the experimental sequence was begun. No spontaneous respiration occurred during the experimental sequence.

The experimental sequence consisted of two parts. One part consisted of introducing variable leaks of known size into the end-tidal CO_2 sampling line at its juncture with the Saracap analyzer sample port while PIP remained constant at the baseline normocapnia level. To vary the size of the leak, a stopcock fitted with an IV catheter plug (heparin-lock type) was placed between the CO_2 sampling line and the CO_2 analyzer sample port. Needles of varying size (27-,

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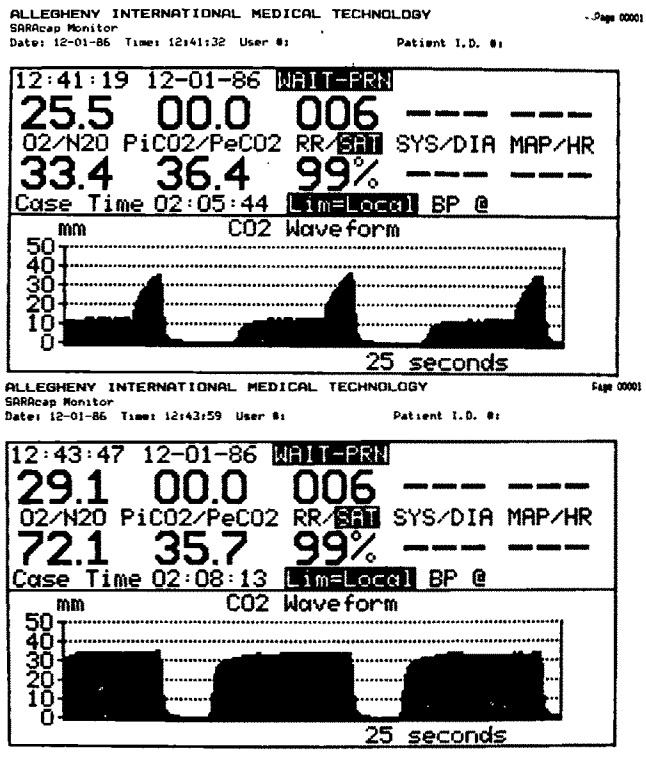

Figure 1. The top panel is a photograph of a CO_2 excretion waveform when the CO_2 sampling line was loosely connected to the CO_2 analyzer sample port. The CO_2 excretion waveform consists of a long low plateau followed by a brief peak. This patient was being ventilated with an inspired O_2 concentration of 30% and an inspired N_2O concentration of 70% (as indicated by flowmeter settings). The bottom panel is a photograph of the CO_2 excretion waveform from the same patient as in the top panel, but when the connection between the CO_2 sample line and CO_2 analyzer sample port was made tight. The CO_2 excretion waveform is now almost square wave or rectangular. Note that the mean exhaled O_2 and N_2O concentrations are now near the inspiratory settings.

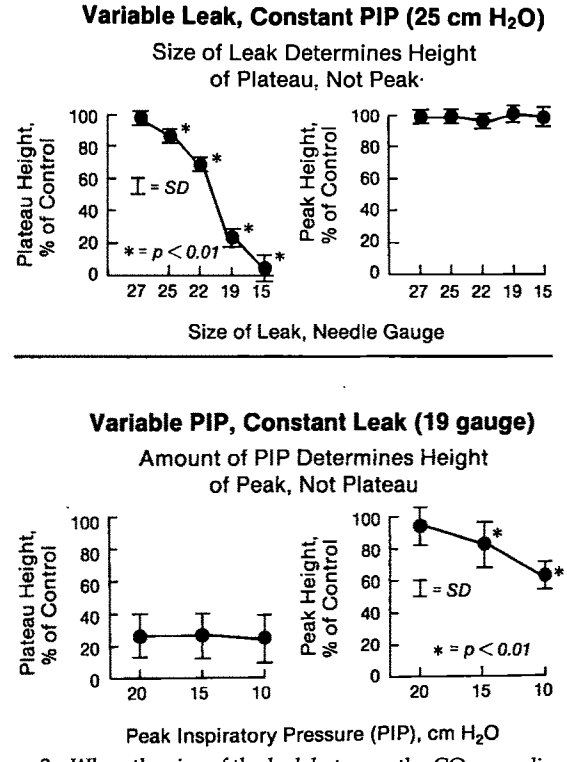

Figure 2. When the size of the leak between the CO_2 sampling line and CO_2 analyzer sample port is increased from 27- to 15-gauge, and peak inspiratory pressure (PIP) is constant at 25 cm H_2O, the height of the long CO_2 plateau progressively decreases (top left panel), whereas the height of the brief CO_2 peak remains constant (top right panel). When the PIP is varied from 20 to 10 cm H_2O, and the leak between the CO_2 sampling line and CO_2 analyzer sample port is kept constant at 19-gauge, the brief CO_2 peak progressively decreases (bottom right panel), whereas the long CO_2 plateau remains constant (bottom left panel).

25-, 22-, 19-, and 15-gauge) were placed in the IV catheter plug to create leaks of known size at constant PIP. Control values (no leak) of end-tidal CO_2 and mean exhalation O_2 and N_2O concentrations were obtained before and after each leak. The values of plateau and peak CO_2 and mean exhalation O_2 and N_2O concentrations during each leak were compared with the mean of these two controls.

The other part of the experimental sequence consisted of causing variable PIP while the leak from the CO_2 sampling line was constant. To vary the amount of PIP at constant leak (19-gauge), tidal volume was changed so that PIP decreased to 20, 15, and 10 cm H_2O. Each 5-cm H_2O decrement required a decrease in tidal volume of about 0.2–0.3 L. Control traces of CO_2 excretion and mean exhalation O_2 and N_2O concentrations were obtained at baseline tidal volume and PIP before and after each reduction in PIP. With each reduction in PIP, the patient was maintained at the decreased PIP for a maximum of five breaths. Therefore, the following control end-tidal CO_2 tension did not increase measurably. All results were analyzed by F-test and Student's paired *t*-test, with $P < 0.05$ considered significant. Results are expressed as mean ± SD.

Results

When the PIP was constant (25 ± 2 cm H_2O for all patients), increasing the size of the leak from 27- to 15-gauge needle size caused a progressive, stepwise, statistically significant decrease in the height of the long CO_2 plateau from 99 to 5% of control (Fig. 2, upper left panel), whereas the height of the brief CO_2 peak varied insignificantly between 101 and 97% of control (Fig. 2, upper right panel). In addition, with increasing leak and constant PIP, mean measured exhalation O_2 and N_2O concentrations progressively and significantly decreased from 39 to 27%, and from 55 to 16%, respectively (Fig. 3, left panel).

When the leak was constant at 19-gauge needle size, decreasing the amount of PIP from 20 to 10 cm H_2O caused a progressive, stepwise, statistically significant decrease in the height of the brief CO_2 peak

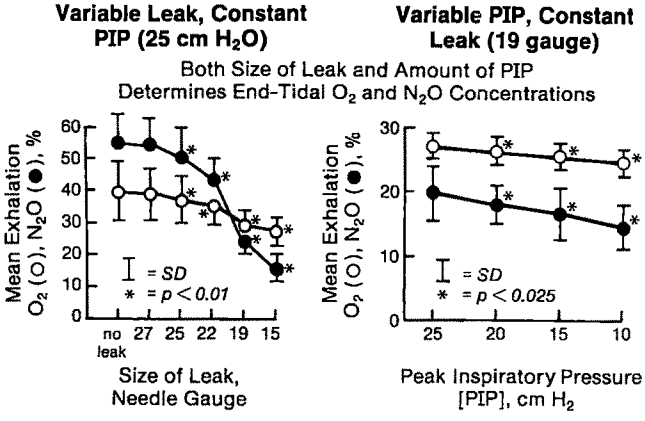

Figure 3. When the size of the leak between the CO_2 sampling line and CO_2 analyzer sample port is increased from 27- to 15-gauge, and peak inspiratory pressure (PIP) is constant at 25 cm H_2O, the mean exhalation O_2 and N_2O concentrations decrease (left panel). When the size of the leak between the CO_2 sampling line and CO_2 analyzer sample port is kept constant at 19-gauge, and the PIP is decreased from 25 to 10 cm H_2O, the mean exhalation O_2 and N_2O concentrations are very slightly, but significantly, decreased.

from 95 to 63% of control (Fig. 2, lower right panel), whereas the height of the long CO_2 plateau varied insignificantly between 26 and 24% of control (Fig. 2, lower left panel). In addition, with constant leak and decreasing PIP, mean exhalation O_2 and N_2O concentrations decreased slightly but significantly (Fig. 3, right panel).

Discussion

We found that the height of the long CO_2 plateau is inversely proportional to the size of the leak, whereas the height of the brief CO_2 peak is unaffected by the size of the leak. In addition, the mean exhalation concentrations of O_2 and N_2O are also inversely proportional to the size of the leak. The greater the size of the leak, the greater the entrainment of room air, the lower the plateau CO_2, and mean exhalation O_2 and N_2O concentrations.

We also found that the amount of PIP determines the height of the brief CO_2 peak, whereas the height of the long CO_2 plateau is unaffected by the PIP. Thus, the next positive-pressure inspiration causes a pressure gradient across the sampling line, resulting in increased flow of undiluted end-expiratory gas in the sampling line (from the previous breath) and less entrainment of room air. The greater the PIP (up to the pressure drop across the sample line produced by the suction pump, which is approximately 30 mm Hg), the greater the flow, the higher the brief CO_2 peak. In further support of this contention is the fact that the brief CO_2 peak in the abnormal waveform occurs regularly with each breath, and has a duration (approximately 1.3 seconds), that is identical to the time it takes to sample (with a flow rate equal to 250 ml/min) the volume of gas in the sampling line (5.5 ml).

The O_2 and N_2O concentration values displayed by the Saracap are mean exhalation values. Thus, with a sample line/sample port leak, the mean exhalation value for O_2 and N_2O will be some weighted average of the plateau and peak values of a true O_2 and N_2O excretion waveform. Because peak value contributes much less to the mean than the plateau value, and the change in PIP affects only the peak value, we observed only small but significant changes in mean exhalation O_2 and N_2O concentrations with change in PIP.

The clinical implications of this study are obvious. First, if the abnormal CO_2 excretion waveform described in this study is observed on an oscilloscope, the connection between the CO_2 sampling line and the CO_2 analyzer should be tightened. However, it should be understood that if the PIP is 20 cm H_2O or greater, then the value of the end-tidal CO_2 concentration during the brief peak of the abnormal CO_2 excretion waveform is not clinically significantly different from the end-tidal CO_2 value obtained when there is no sample line/CO_2 analyzer connection leak. Second, if only a digital readout is available (no oscilloscopic excretion waveform), and the digital readout seems inappropriately low, then the integrity of the CO_2 sampling line/CO_2 analyzer sample port connection should be checked. Finally, if the O_2 and N_2O exhalation concentrations are inappropriately low compared to the known inspired values, then the integrity of the sample line/sample connection should be checked. In all of these situations, making a rational decision (changing ventilation, concentration of inspired gases) based on erroneous end-tidal data can only result in an inappropriate response.

In summary, when there is a loose connection between an end-tidal CO_2 sampling line and the CO_2 analyzer (Saracap), the CO_2 excretion waveform is very unusual and consists of a long plateau followed by a brief peak, rather than the usual square CO_2 excretion waveform. The long CO_2 plateau is caused by entrainment of room air through the leaky connection by the continuous CO_2 analyzer suction, and the brief CO_2 peak is caused by the next PIP, which transiently pushes undiluted end-tidal gas through the sampling line into the CO_2 analyzer. Because the O_2 and N_2O values digitally displayed by the Saracap are mean exhalation values, the O_2 and N_2O concentrations are a function of both the size of the leak and the PIP.

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Improvement of Intraoperative Somatosensory Evoked Potentials by Etomidate

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Key Words: ANESTHETICS, INTRAVENOUS—etomidate. MONITORING—somatosensory evoked potentials. BRAIN—somatosensory evoked potentials.

Use of somatosensory evoked potentials (SSEPs) for monitoring of the nervous system during corrective surgery on the spine has stimulated interest in the effect of anesthetics on SSEPs. Inhalation anesthetics have generally demonstrated a dose-dependent depression of amplitude and increase in latency, with intravenous agents generally showing lesser depression of amplitude and latency. This suggested to many that a narcotic-based anesthetic technique may be superior when monitoring patients with low-amplitude evoked responses.

A particular monitoring challenge occurs in patients in whom preexisting neural abnormalities may make monitoring difficult. These patients may be at greater risk for neural complications, making monitoring most important at a time when it is also most difficult (1). As with the following case, the intraoperative evoked responses may be too poor to be reliably monitored. An anesthetic that would increase the amplitude of evoked responses might make the response usable for monitoring. Etomidate may be such an agent. As shown in several studies (2–6), etomidate increases the amplitude of cortically derived median nerve SSEPs. We now report a case in which the introduction of etomidate during a narcotic anesthetic improved SSEPs responses from posterior tibial nerve stimulation and allowed the patient's neural function to be monitored when it would otherwise have been considered unreliable.

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Case Report

An 80-kg, 60-year-old man presented for posterior spinal decompression and placement of Cottrell–Dubosset instrumentation with autologous bone graft. This was planned for correction of scoliosis and subluxation of L2 on L3, thought to be the result of two previous laminectomies for spinal stenosis. Clinically, the patient had severe bilateral back pain radiating to both legs; the right leg was more severely affected than the left. The patient was premedicated with an intramuscular injection of morphine 10 mg and midazolam 2 mg 45 minutes before the procedure. Anesthesia was induced with IV midazolam 15 mg and alfentanil 8.0 mg in three divided doses. Vecuronium 5 mg was given after determination of somatosensory motor threshold (see later) and the trachea was intubated. The patient was placed on the operating table with appropriate padding, and anesthesia was continued using infusions of alfentanil (1.5–2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), midazolam (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and vecuronium (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The lungs were mechanically ventilated with a 50:50 mixture of air and oxygen. End-tidal carbon dioxide tension was maintained at 34–38 mm Hg.

SSEPs from posterior tibial nerve stimulation were recorded using a Nicolet CA 1000/DC 2000 (Nicolet Biomedical Instruments, Madison, WI). Sterile 11-mm, 27-gauge subdermal needle electrodes for stimulation were inserted over the nerve at the ankle after the induction of anesthesia and before neuromuscular blockade. Appropriate motor responses were elicited from the left and right legs with 5 and 7 milliamperes (mA) constant current (300 microsecond square wave impulse), respectively. Similar needle electrodes were placed over the posterior spinous process of C7 (SC-7) and at F_z and C_z' (International 10–20 system locations with C_z' located 2 cm posterior to C_z) for recording purposes. A silver–silver chloride grounding plate was placed on the right shoulder. All electrode impedances were between 3 and 4 kOhm. Initial evoked response recordings using 10 mA con-

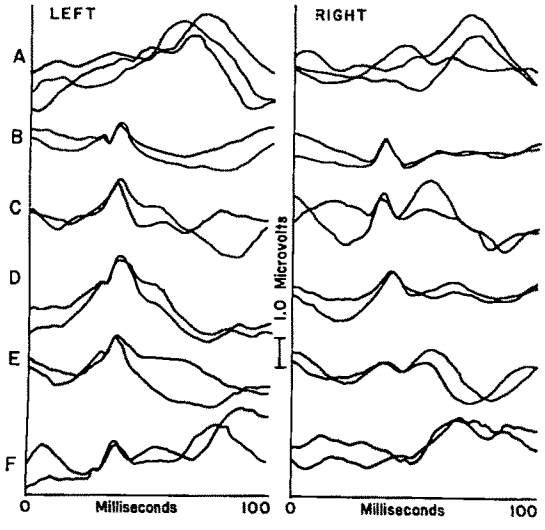

Figure 1. Representative intraoperative SSEP tracings. Evoked responses from left and right posterior tibial nerve stimulation are shown. A positive response at the active electrode is plotted upward. The three responses shown in **A** were recorded before administration of etomidate and demonstrate inability to replicate. The responses shown in **B** are after the initial administration of etomidate. The response shown in **C**, **D**, and **E** represent the responses at 1.5, 3, and 10 hours after the administration of etomidate. The final responses are shown in **F** and have the right-sided abnormality, as indicated in the text.

stant current at a rate of 5.6 Hertz (Hz) and bandpass filtration of 5–250 Hz failed to demonstrate a repeatable response (Fig. 1**A**). A review of the equipment and recording techniques failed to identify a reason for the poor quality of the response. The EEG, however, revealed an appropriate signal without unusual interference or artifact. Attempts to produce a repeatable signal by slowing the stimulation rate (to 3.7 Hz), increasing the stimulation pulse width (to 500 microseconds) and current (to 19.9 mA) or increasing the bandwidth of the amplifiers and increasing the poststimulus analysis window to (150 milliseconds) failed to produce repeatable responses. The presence of a late cortical peak was suggested, but reliance on this for monitoring was not considered adequate because of variability.

Because monitoring was considered highly desirable in this case, an attempt to amplify the response utilizing etomidate was made. Without any change in patient management other than the continued surgical dissection of paraspinous muscles from the posterior spinal elements, 40 mg of etomidate (0.5 mg/kg) was infused IV over 3 minutes. During this time, there were no hemodynamic changes. Within minutes, the evoked responses were easily elicited and clearly visible using the original techniques for recording and stimulation (Fig. 1**B**). As this response remained reproducible on several trials, the anesthesia management was altered by discontinuing the midazolam infusion and infusing etomidate at 46 mg/hr (0.01 $mg \cdot kg^{-1} \cdot min^{-1}$) (7). At no time was the cervical spinal response reproducible (before or after the etomidate).

The responses at 1.5, 3, and 10 hours (**C**, **D**, and **E**, respectively) after the etomidate are shown in Figure 1. The evoked responses could be reliably monitored up to the time of placement of instrumentation, after which they deteriorated. At that time, the evoked responses from the right leg increased in latency and decreased in amplitude. This was followed by deterioration of the response from the left leg as well. The infusions were discontinued and a wake-up test was conducted. When the patient was awakened, the severe bilateral SSEP deterioration was accompanied by the absence of motion in both legs. Anesthesia was reestablished, and the instrumentation was adjusted. This was followed by the return of repeatable cortical responses from stimulation of the left leg and repeatable late cortical responses from the right leg (Fig. 1**F**). A second wake-up test was performed and revealed bilateral leg motion. The procedure was completed. The patient awoke with severe sensory deficits in the right leg without apparent motor deficits. At discharge 21 days later, these were resolved.

Discussion

The ideal anesthetic for SSEP monitoring has not been identified. The anesthetic technique initially used for the procedure reported here had also been used many times previously to monitor comparable patients undergoing similar procedures. However, in this case reproducible responses could not be elicited clearly. The ability to establish and maintain reproducible and reliable responses with the use of etomidate contributed to reliable SSEP monitoring and provided a means for the detection of two periods of potential neural damage.

In this case, the initial improvement in the evoked response was thought to be a consequence of the introduction of etomidate. No other anesthetic management changes were introduced during or after the period of signal improvement. Thus, at the time the evoked responses improved the patient was receiving alfentanil and midazolam infusions, as well as the etomidate. During this period, there were no other physiologic changes that could have contributed to an improvement in the response. Ventilation with air:oxygen was unchanged and end-tidal carbon dioxide tensions remained between 34 and 38 mm Hg. There were no apparent changes in oxygen tensions

and pulse oximetry of the hand showed arterial oxygen saturation remained in excess of 98%. Blood pressure remained unchanged and there were no apparent fluctuations in central blood volume. Body temperature (nasopharyngeal) remained between 35.4 and 35.7°C.

There were no indications of potential cerebral ischemia when the responses were poor, and head, neck, leg, and spine positioning remained unaltered. During this period, the surgical procedure consisted of progressive dissection of the paraspinous muscles from the posterior lamina of the vertebrae. The surgeon felt that it was unlikely that any significant alteration could have occurred in spinal positioning or blood flow during the period of improvement.

In the absence of other explanations, the improvement in signal quality appears related to the etomidate infusion. The increase in amplitude in this study is similar to that seen in several other studies of the effect of etomidate on short latency SSEP. Kalkman et al. (4) gave etomidate 0.3 mg/kg after infusion at a rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ for 10 minutes to patients premedicated with morphine and atropine and observed a 2.6-fold increase in amplitude of median nerve cortical responses (N_1P_1). McPherson et al. (3) noticed a 2- to 12-fold increase in median nerve cortical SSEP amplitude after a bolus (0.3 mg/kg) and subsequent infusion (0.1 $mg \cdot kg^{-1} \cdot min^{-1}$) of etomidate. Thornton et al. (5) evaluated auditory-evoked responses using an infusion of etomidate that was increased stepwise in increments from 0.01 $mg \cdot kg^{-1} \cdot min^{-1}$ to a maximum of 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$. They saw no change in brainstem responses but noticed a decrease in amplitude of the cortical response (N20–P23) from median nerve stimulation. The responses increased approximately 2.15-fold when 0.3 mg/kg etomidate was given to patients anesthetized under neuroleptanesthesia with fentanyl.

These studies (2–4,6) also revealed an increased latency of the short latency cortical responses after etomidate administration. In our present case, a latency change could not be quantitated due to failure of the responses to replicate before the administration of etomidate. In contrast to the changes in the cortically derived peaks, three studies (2,3,6) observed no significant increase in cervical response amplitude. The failure of "amplification" of this response may account for the lack of reproducibility of our cervical spinal response after the etomidate. These are consistent with a site of action for this effect cephalad to the spinal cord.

The mechanism of this increase in activity is not known. However, if amplitude represents an index of the number of neural units firing or the synchrony of firing, this may represent an alteration of the balance of inhibitory and excitatory influences in the thalamocortical tracts thought to generate these waves (8). Alternatively, this phenomenon may suggest that etomidate enhances the excitability or irritability of the neural system in this portion of the central nervous system. Enhancement by irritability has been suggested by Winters et al. (9). Consistent with this is the observation that etomidate produces myoclonic activity. If indeed this is a result of an unstable state, then alteration of evoked response morphology might occur as is seen with γ-hydroxybutyrate (8). That this effect is due to the etomidate and not the carrier vehicle (35% propylene glycol) has previously been demonstrated (3).

Regardless of the mechanism of action, etomidate was safely administered during this anesthetic without adverse hemodynamic consequences. To date, no studies have been done to determine which patients may not tolerate the addition of such a drug to a general anesthetic. It is, however, notable that adrenocortical suppression occurs with etomidate. Depression of aldosterone, cortisol, and dehydroepiandrosterone has been observed after bolus and infusion etomidate techniques with return to normal levels between 8 and 24 hours after drug delivery (10,11). Clinical sequelae of operative use have not been reported as with prolonged infusions in intensive care (12), and the need for exogenous intravenous steroid administration has been questioned (13). In our patient, dexamethasone 20 mg was given as a planned component of the surgical procedure.

McPherson et al. (3) expressed concern about induction of anesthesia in patients using etomidate due to the transient nature of the increase in SSEP amplitude. Our case suggests that the increase may be sustained when a continuous infusion follows a bolus injection. Except during the period of deterioration and during the wake-up tests, the amplitude was sustained for the duration of surgery (12 hours). At the time of deterioration, the etomidate infusion had not been disconnected or stopped. This, in addition to the observation that the change was initially asymmetric (i.e., right more than left) suggests it was not an anesthetic induced deterioration that would be expected to affect each side similarly.

We have observed this effect (i.e., an increase in amplitude) during a general anesthetic in other cases. However, we feel this case is significant because monitoring might otherwise have been unreliable or abandoned. This case is also notable in that the enhancement was sustained during the entire period of infusion. As suggested by Kalkman et al. (4), this

may make etomidate a desirable drug to use during procedures when SSEP monitoring is required in patients who have exceptionally small evoked potentials. However, the importance of a constant infusion must be stressed as changes in the etomidate level may make marked changes in amplitude and latency due to its short pharmacodynamic duration of action.

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Submocusal Emphysema with Airway Obstruction From Nasal Oxygen Cannula

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Key Words: COMPLICATIONS, EMPHYSEMA—subcutaneous. OXYGEN—nasal.

Gases delivered under pressure to the airway can enter a break in the mucosa and dissect through tissue planes to cause subcutaneous and submucosal emphysema (1–3). Following is a report of complete upper airway obstruction due to submucosal emphysema caused by mucosal perforation with a nasal oxygen cannula in the recovery room.

Case Report

A 66-year-old man with hematuria was scheduled for cystoscopy and prostate biopsy. He was a one pack per day smoker but otherwise healthy and active.

In the operating room he was preoxygenated, anesthesia was induced with 300 mg thiopental, and the patient was allowed to breathe nitrous oxide, oxygen, and isoflurane spontaneously by mask. There was a brief episode of coughing on induction but the remainder of the 15-minute operative course was smooth.

At the end of the operation, he breathed 100% oxygen for 2 to 3 minutes until awake and was then transferred to the recovery room. A single plastic cannula (4 mm OD) was gently inserted 2 cm into the right nostril to deliver supplemental oxygen at 3 L/minute. Within a minute the patient attempted to sit up, at which point the right side of the face was seen to be rapidly enlarging. The nasal cannula was immediately removed, but his airway was already completely obstructed. Visualization with a laryngoscope, though difficult, revealed normal-appearing epiglottis and laryngeal mucosa, but the pharynx and uvula were so swollen with submucosal emphysema that the tongue was displaced and protruding from the mouth. His trachea was intubated enabling easy ventilation.

A chest x-ray revealed pneumomediastinum and right pneumothorax requiring chest tube placement. The right nostril was swollen closed, and patient discomfort prohibited a search for the point at which the cannula presumably perforated the mucosa.

By the following morning the subcutaneous emphysema of his face and neck and submucosal emphysema in the pharynx had resolved so his trachea was extubated, allowing spontaneous ventilation with ease. The pneumothorax sealed the following day, enabling removal of the chest tube. The patient recovered completely without deficit or disability and returned weeks later for an uneventful suprapubic prostatectomy for his prostate cancer.

Discussion

Pneumothorax resulting from positive-pressure ventilation may be associated with subcutaneous emphysema sometimes covering much of the body. The route by which the air dissects is described and illustrated by Dripps et al. (Fig. 33–2 in [4]) and by Mauder et al. (2). Submucosal emphysema of the mouth and pharynx is familiar, especially to oral surgeons, and can extend to the chest (1–3,5). Some readers may have found that a nasogastric tube that passed with difficulty was actually dissecting submucosally down the pharynx in the tissue plane where air was presumed to have traveled in the present and other cases.

The nasal cannula in this case provided supplemental oxygen in a seemingly noninvasive manner, but this case reveals yet another means by which submucosal air can enter—and at terrifying speed. The wall-mounted oxygen flowmeter, which receives a 50 lb/in.^{2} supply, is designed to regulate flow in the absence of a downstream obstruction, but an obstruction will allow pressure in the tubing to approach that of the supply.

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The single cannula for nasal oxygen had been in use for years at this hospital without any such problem having been identified, although problems of this type though lesser in degree may have occurred without being recognized, as suggested by Orr (5). We no longer use this device for nasal oxygen delivery and urge abandonment of it by those who may not have done so already. All anesthesiologists will want to be aware of the potential for submucosal emphysema of the upper airway, regardless of its frequency, because of its seriousness. The present case in which a nasal oxygen cannula caused submucosal emphysema (as well as pneumomediastinum and pneumothorax) resulting in life-threatening upper airway obstruction emphasizes the need to be aware of the risk of submucosal emphysema when gases are delivered under pressure to the upper airway.

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Succinylcholine-Induced Idioventricular Rhythm

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Key Words: HEART, ARRHYTHMIAS—idioventricular. NEUROMUSCULAR RELAXANTS—succinylcholine.

Idioventricular rhythm (IVR) is characterized electrocardiographically by regularly occurring wide QRS complexes at rates between 30 and 100 beats/min in the absence of regularly conducting P waves (1,2). IVR, which has also been called accelerated ventricular rhythm, idioventricular tachycardia, slow ventricular tachycardia, and accelerated isorhythmic ventricular rhythm, may, at rates faster than 60 beats/min, be difficult to distinguish from atrioventricular (AV) nodal or junctional tachycardia with aberrant ventricular conduction. Except in the settings of an acute myocardial infarction or digitalis toxicity, the occurrence of IVR is distinctly uncommon and has not previously been reported to have occurred during anesthesia (3,4).

Case Report

A 37-year-old 73-kg man with aortic stenosis due to a congenital bicuspid valve was scheduled to undergo excision of a maxillary cyst and a supernumerary molar under general anesthesia. Cardiac catheterization 10 years previously demonstrated a 50-mm Hg gradient across the aortic valve, but normal ventricular function; the patient was asymptomatic and had not been prescribed any medication.

General anesthesia was deemed necessary after a prior attempt to extract the cyst and tooth using local anesthetic infiltration had been abandoned when the patient became bradycardic and syncopal. Recovery was prompt and required no treatment; an ECG and chest x-rays obtained subsequently were normal.

After receiving prophylactic antibiotics but no sedative premedication, the patient was given fentanyl 75 μg IV while being denitrogentated with 100% O_2. Anesthesia was induced with thiopental 400 mg IV, and succinylcholine 100 mg IV was used to facilitate tracheal intubation. With the aid of Magill forceps, a 7.0-mm ID nasotracheal tube was placed endotracheally but was removed promptly when the balloon cuff, which had ruptured from instrumentation, could not be made to seal the trachea. Halothane 1% and O_2 were administered by mask to maintain anesthesia and, in preparation for reintubation, atropine 0.2 mg IV was given to prevent second-dose succinylcholine-induced bradycardia.

One minute later, after the heart rate had increased from 64 to 70 beats/min, administration of succinylcholine 90 mg IV caused the cardiac rhythm, as monitored on lead 2, to change from a sinus mechanism to that of IVR at 44 beats/min (Fig. 1). Systemic blood pressure (measured by arm sphygmomanometry) decreased from 130/80 mm Hg to 110/70. Immediate treatment with atropine 0.4 mg IV resulted in rapid reversion to sinus rhythm at 68 beats/min and a return of blood pressure to 130/80. Nasotracheal intubation was achieved and the remainder of the anesthetic was uneventful.

Discussion

Although controversy persists, paroxysmal ventricular tachycardia and IVR appear to be separate and distinct entities with differing mechanisms, therapies, and prognoses (1–4). The former is characterized by the abrupt onset of ventricular rates between 120 and 180 beats/min, is considered to be caused by a reentry phenomenon, often in the setting of an irritable ectopic ventricular focus, and may result in hemodynamic deterioration and the development of ventricular fibrillation. Treatment with lidocaine, quinidine, or procainamide are advised; cardioversion may be required, particularly in the setting of an acute myocardial infarction.

IVR, on the other hand, is characterized by a gradual onset in the setting of sinus bradycardia,

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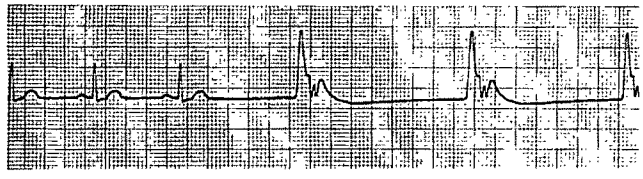

Figure 1. Simulated electrocardiographic tracing, illustrating the transition from sinus rhythm at 70 beats/min to that of idioventricular rhythm at 44 beats/min observed in the case presented.

with ventricular rates <100 beats/min and a duration of several minutes or less. Ventricular escape rhythms at rates between 20 and 50 beats/min fall within this category. Such rhythms are thought to result from slowing or blockade of the sinoatrial (SA) and the AV nodes and, occasionally, acceleration of infrajunctional pacemakers. These rhythms, even in the context of an acute myocardial infarction, are self-limited, do not usually cause or portend serious hemodynamic deterioration, and generally require no treatment (2,4). When loss of the atrial contribution to cardiac output results in inadequate circulatory performance, therapy consists of giving an anticholinergic drug such as atropine (5) to increase the firing of supraventricular pacemakers, particularly the SA node. Treatment with lidocaine and other antiarrhythmics or cardioversion is not indicated.

This patient's presentation of IVR is consistent with ventricular escape in the setting of marked vagal slowing of the SA and AV nodes. The administration of two doses of succinylcholine in succession, particularly between 4 and 5 minutes apart, has been established as causal for a variety of bradyarrhythmias, including sinus bradycardia, sinus arrest with asystole, junctional rhythm, and Wenckebach phenomena (6,7). Sensitization of the cardiac muscarinic receptors by the first dose of succinylcholine (through its metabolite succinylmonocholine) has been postulated to explain the pronounced vagal stimulation induced by the second dose of succinylcholine (8,9). In these circumstances, IVR, though unusual, may be considered a variant response to second-dose succinylcholine administration.

The significance of its occurrence lies principally in its immediate hemodynamic consequences, because IVR tends not to deteriorate into more serious arrhythmias. Consequent to the development of IVR, the loss of sequential atrioventricular contraction may result in decreased cardiac output of 20% or more. In this case, cardiovascular performance was not severely compromised. Given the setting of marked vagal stimulation, however, the possibility that this patient's rhythm might slow further to the point of cardiac arrest led us to intervene. Treatment with atropine promptly eliminated the ectopic ventricular rhythm by opposing the vagal effects and accelerating the sinus rate, thus restoring sinus rhythm.

The unusual development of IVR in this case, rather than sinus bradycardia, may have been partially due to concurrent halothane administration. Experimentally, Tucker and Munson (10) showed that succinylcholine markedly increases the ventricular arrhythmogenicity of epinephrine in dogs anesthetized with halothane. In the presence of vagally mediated supraventricular slowing, catecholamine release from tracheal intubation, despite the absence of hypoxia or hypercarbia, may be sufficient to induce ventricular irritability. Nevertheless, the origins of IVR under these circumstances are vagal, and its treatment with atropine is rational and appropriate.

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Tracheal Intubation in Children: A New Method for Assuring Correct Depth of Tube Placement

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Key Words: ANESTHESIA—pediatric.
INTUBATION, TRACHEAL—pediatric

Airway mismanagement is a major factor responsible for morbidity and mortality in pediatric anesthesia. One of the most feared complications is accidental intraoperative tracheal extubation in a paralyzed patient receiving controlled ventilation. Less potentially catastrophic, but nevertheless undesirable, is unrecognized bronchial intubation. Accurate placement of the endotracheal tube (ETT) to a predetermined depth is thus of prime importance. After the head has been positioned for the operation, the tip of the ETT should, in our opinion, be located 2.0 cm above the carina in the neonate, infant, and young child. In children approaching 5 to 6 years of age, this distance may be increased to 3.0 cm. We want to be as sure as possible that the tip of the ETT lies a safe distance above the carina and well below the vocal cords. We describe a simple and effective clinical method for achieving this in pediatric patients.

Methods

We collected data from 41 pediatric patients to whom general anesthesia had been administered for placement of central lines via the subclavian approach. The patients varied in age from 1 day to 10 years (mean 2.72 years), in weight from 2.0 to 28.0 kg (mean 11.0), and in height from 45.0 to 135.0 cm (mean 80.87). After induction of anesthesia and neuromuscular blockade, all patients were intubated with the ETT placed with the head in the appropriate position as described below, and securely taped at the mouth. A chest radiograph is routinely ordered at the end of this operation before extubation to exclude pneumothorax, and this provided us with the opportunity to measure the depth of tube placement to verify the accuracy of our technique. We were unable to measure the distance between the tip of the ETT and the larynx because, with the ETT in situ, it was not possible to define the position of the larynx accurately enough to generate reliable data. Institutional approval was not required for the purposes of this study because there was no deviation from routine procedures.

We use Mallinckrod uncuffed ETTs with a right-sided Murphy's eye and a bevel facing to the left. This latter feature accounts for the fact that the tip of the ETT invariably enters the right mainstem bronchus when advanced beyond the carina (1). After tracheal intubation and with the head in the anatomically neutral position, we manually ventilated the patient and auscultated both lung fields in the midaxillary line and over the epigastrium to confirm that the ETT was in the trachea. The ETT was then gently advanced until it entered a mainstem bronchus, usually on the right. This event was confirmed by three clinical observations. Bronchial intubation is accompanied by loss of breath sounds, usually on the left side, best assessed in the midaxillary line, unilateral decrease in thoracic cage movement, best observed in the subclavicular areas, and a distinct decrease in compliance readily appreciated during manual compression of the reservoir bag. The ETT was then slowly withdrawn until bilaterally equal breath sounds returned, chest movement became bilaterally equal, and there was sudden improvement in compliance at which point the end of the ETT, having just emerged from the mainstem bronchus, was at the carina. The ETT was steadied in this position while the mark on the ETT opposite the upper gum or teeth was recorded as the mouth-to-carina distance. If the head was to be in the "neutral" position for the operation, the ETT was withdrawn a further 2 cm before being secured. However, if it was required that the head be in other than the neutral position,

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we positioned the head in the anticipated operative position before carrying out the maneuver described earlier. We had no instance of accidental extubation, either during this study or at any other time using this technique. It is applicable to both oral and nasal intubation.

Results

In the patients studied, the distance from the tip of the ETT to the carina ranged from 1.75 to 3.0 cm with a mean of 2.07 cm (SD ± 0.24). By the one-sample *t*-test, this was not significantly different ($P \geq 0.08$) from the 2-cm distance we aimed to achieve. There was a statistically significant correlation between the mouth-to-carina distance and patient height ($r = 0.909$) by linear regression analysis. Patient age ($r = 0.847$) and weight ($r = 0.880$) were less strongly correlated with mouth-to-carina distance. We did not consider radiological image magnification a variable, because it applied to all patients.

Discussion

If the length of the trachea in the pediatric patient could be reliably related to a variable such as age, weight, or height, it would be easier to determine the depth to which an ETT should be inserted. However, reports of studies on the length of the trachea in the pediatric age group are confusing. The earlier data were obtained from Hall's study of cadavers (2), whereas, in the living, the trachea is longer and its length and diameter vary with respiration (3). Hall's often-quoted study of patients from birth to 18 months of age was made during rigid bronchoscopy "with the head in a relatively neutral position." However, the illustration accompanying his article shows the measurements being made using a rigid bronchoscope and with the neck in full extension, in which position the larynx has been shown to move cephalad in the adult from C5 to C4. Hall's data are thus open to criticism, but if one accepts that the error was a constant one then it is worth noting that the author found the tracheal length to vary from 5.0 to 7.0 cm in the first 3 months of life and from 7.0 to 9.0 cm between the ages of 12 to 18 months. In other studies, the range of tracheal lengths in neonates, ranging in maturity from premature to full term, has been reported to be 3.0 to 6.0 cm (2–5). It is therefore not surprising that there have, over the years, been many suggestions for ways to solve the problem of safe depth placement. These have included formulas and tables based on body size or gestational age (3,4,6–9), measured markings on the distal end of the ETT (6,10), palpation at the suprasternal notch during insertion of the tube (11), use of a special ETT with a fiberoptic light at the tip to identify the tube tip by transillumination after intubation (12), and impedance pneumography with oscilloscopic display (13). Tochen's study (14), in which he proposed the rule of 7-8-9, was confined to newborn infants weighing 0.7 to 4.1 kg and therefore provided no guidelines for older children. Some standard texts do not venture a discussion of the subject (15,16), and we agree with Smith, who concludes that "anatomic variations again prove too great to allow reliance on any predetermined reference scale" (7).

Moreover, once an ETT has been inserted and secured at the lips, the distal tip moves caudad with neck flexion and cephalad with neck extension (17,18) or rotation (10). In a radiologic study of three neonates, flexion of the neck caused the ETT to advance caudad a maximum of 0.5 cm, and on rotation of the head the tip of the ETT moved cephalad a maximum of 1.2 cm (10). Another radiologic study of 16 neonates (19) showed that movement of the tip of the ETT when the position of the head was changed from full flexion to full extension ranged from 0.7 to 2.8 cm. The mean range of movement of an orotracheal tube was 1.43 cm ± 0.48 SD and that of a nasotracheal tube was 1.68 cm ± 0.59 SD. Based on this information, it has been our practice to attempt to place the tip of the ETT 2 cm above the carina in neonates, infants, and small children. It would seem reasonable to increase this distance to 3 cm in children over 5 years of age.

Other authors working in intensive care areas have found that the clinical signs we describe are unreliable for detecting endobronchial intubation (10). In the operating room we have had no difficulty in making the diagnosis clinically. We think this is because we deliberately seek it out with the aid of manual positive-pressure ventilation and the clinical signs mentioned earlier. In addition, our patients nearly always have little or no pulmonary pathology, making the detection of changes in breath sounds easy.

We have seen no clinical evidence that careful controlled advancement of the tip of the ETT into a mainstem bronchus for a few seconds is harmful. A new fiberoptic catheter with an external diameter of 2.6 mm has recently become available (Microvasive, Inc., Milford, MA, Catalog no. 8320). We have used it in ten patients to examine the carinal area after deliberate endobronchial intubation and have seen no evidence of trauma. In many years of experience

in a busy pediatric service, there have been no accidental extubations or inadvertent endobronchial intubations.

Davies and Munro (20) and Bloch (21) described endobronchial intubation to estimate ETT depth but did not produce evidence to verify the efficacy of their techniques. We present our data as evidence that initial endobronchial intubation can be used safely and effectively to position the ETT 2.07 cm (± 0.24) above the carina in pediatric patients. We have been able to dispense with a portable radiograph, saving time and avoiding unnecessary exposure; in particular, it eliminates the expense, which in our hospital amounts to $110 per patient.

In summary, we describe our routine technique for placing the ETT to a predetermined depth after endotracheal intubation in pediatric patients. To validate its accuracy, we studied 41 pediatric patients from 1 day to 10 years old in whom the placement depth was measured on a routine chest x-ray film taken at the end of the operation. The measured distance from ETT tip to carina ranged from 1.75 to 3.0 cm (mean 2.07, SD ± 0.24). This was not significantly different ($p>0.06$) from the distance of 2 cm we wished to achieve. There was a weak but statistically significant correlation ($r = 0.909$) between height and measured distance. This simple clinical maneuver is applicable to children of all ages for either oral or nasal endotracheal intubation and requires no equipment other than a stethoscope. We therefore recommend its routine use in pediatric patients, where the margin for error is small.

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Prolongation of the Inspiratory Phase in the Treatment of Unilateral Lung Disease

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Key Words: VENTILATION, ARTIFICIAL—prolonged inspiration. LUNG, DISEASES—artificial ventilation.

Severe unilateral lung disease presents unique management problems. Several innovative interventions have been described, including independent synchronous ventilation (1), asynchronous ventilation (2), and high-frequency jet ventilation (3). The following case illustrates how alterations in peak flow and waveform with the addition of an inspiratory pause may yield to significant improvement in arterial oxygenation. To our knowledge, this is the first report suggesting a beneficial application of a long inspiratory phase in the treatment of unilateral lung disease.

Case Report

A male in his mid-thirties was admitted to the Neurosurgical Intensive Care Unit of our institution for severe head and bilateral lower-extremity trauma sustained after a motor vehicle accident. At the scene of the injury an oral tracheal tube had been inserted and resuscitative measures were employed to reverse cardiovascular collapse. On admission his Glasgow Coma Score was 6, cranial CT scan showed minimal epidural hematoma, and chest x-ray (Fig. 1) was reported as clear. He was treated with mechanical hyperventilation, osmotic diuresis, and leg traction for his lower-extremity fractures. Three days after hospitalization, he suddenly developed fever and hypoxemia; a chest x-ray revealed a right panlobar pneumonic process believed to be secondary to aspiration (Fig. 2). Arterial blood gas tensions at this time showed marked hypoxemia, which was refractory to increasing the $F_{I_{O_2}}$. Increased levels of PEEP likewise did not improve, but rather worsened Pa_{O_2}. Table 1 indicates initial and all subsequent blood gas tensions.

We made the following ventilator (Bennett 7200a, Puritan-Bennett Corp., Los Angeles CA) adjustments at this time: a reduction of peak flow from 60 to 40 L/min, a change of waveform from constant to decelerating flow pattern, and the addition of an end-inspiratory pause of 1 second. These maneuvers altered the inspiratory/expiratory ratio from 1:2 to 2:1. Peak airway pressure decreased from 35 to 25 cm H_2O, and there was immediate improvement in arterial oxygenation. These maneuvers permitted an increase in tidal volume from 700 to 900 ml, a more appropriate value of 12 ml/kg, without altering peak airway pressure. $F_{I_{O_2}}$ and PEEP could subsequently be decreased; over the next 48 hours, he was eventually weaned to CPAP 5 cm H_2O with $F_{I_{O_2}}$ of 0.3. His pneumonic process thereafter responded to antibiotics, and he has had slow improvement in neurologic status.

Discussion

Severe unilateral lung disease poses the challenge of improving the ventilation and perfusion characteristics of the diseased lung without adversely affecting the normal lung. Techniques of improving $\dot{V}/\dot{Q}$ abnormalities in bilateral disease such as PEEP can prove ineffective and actually deleterious when simultaneously applied to both lungs. Our case is similar to previous reports (1–4) of patients with unilateral lung disease whose blood gas tensions deteriorate with increases in PEEP levels. A simple and, in many cases, successful maneuver is to elevate the affected lung; we were unable to do so, however, because of the patient's skeletal traction. A more aggressive approach is to selectively intubate the diseased and normal lungs and apply differential lung ventilation. This technique, however, poses problems of mechanical complexity and requires se-

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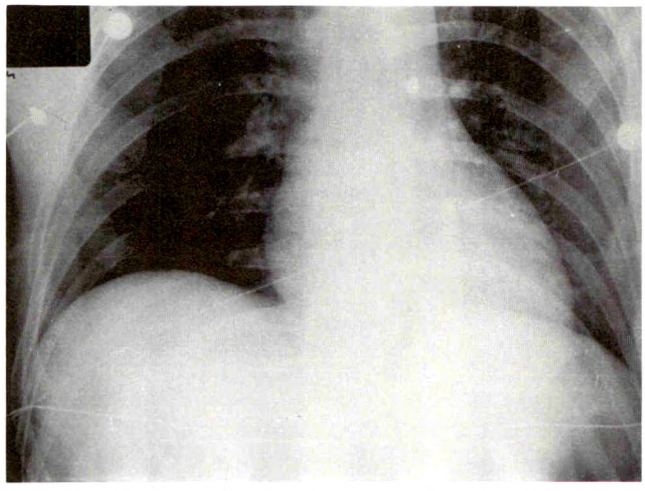

Figure 1. Admission chest x-ray revealing clear lung fields.

dation and paralysis, both undesirable in a neurologically injured patient. We chose to prolong the inspiratory phase in an effort to equalize the distribution of gas between the affected and normal lung by the use of two techniques that have been individually shown to improve distribution of ventilation.

Al-Saady and Bennett (5) compared decelerating gas flow and constant flow with the same inspiratory time. They noted improvement in total compliance and oxygenation, with decreases in airway resistance, peak airway pressure, and VD/VT. They concluded that decelerating flow improves gas distribution, particularly to areas of the lung with prolonged time constants.

The addition of an end-inspiratory pause also facilities equilibration of disparate lung regions. Fuleihan et al. (6) observed significant decreases in VD/VT and $Paco_2$ with an end-inspiratory pause of 0.6 and 1.25 seconds, compared with a zero end-inspiratory pause.

Unilateral lung disease results in lungs with different compliance characteristics. When measurement of compliance is made using a single-lumen tracheal tube, total compliance will be greater than the mean of the individual compliances of the lungs, if measured separately. This is because during conventional ventilation, the majority of tidal volume is delivered to the compliant, i.e., unaffected, lung. The resultant increase in alveolar pressure compresses the pulmonary vascular bed of the normal lung, causing both redistribution of blood flow to the diseased lung and increases in pulmonary venous admixture and deadspace. By prolonging the inspiratory phase, we believed that ventilation of the affected lung would improve, and that maldistribution of blood flow would be lessened because of lower peak airway pressure.

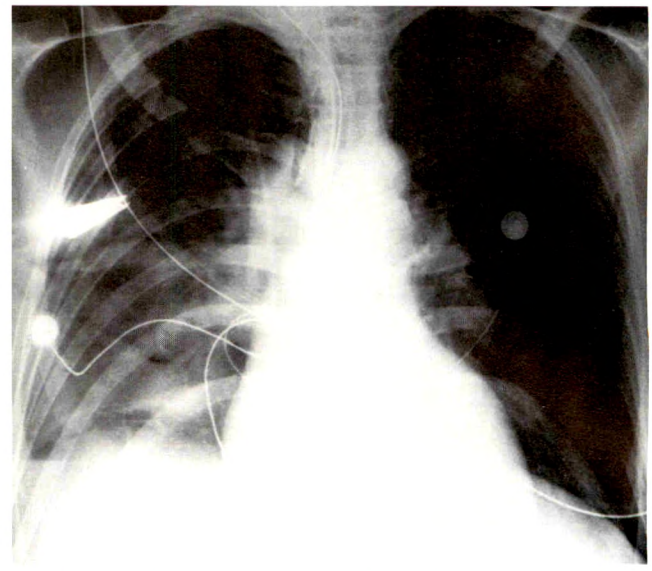

Figure 2. Chest x-ray demonstrating severe right unilateral pneumonic process. In addition, blunting of the right costophrenic angle was noted.

Whether peak or mean airway pressures is the more important determinant of such maldistributed blood flow remains controversial (7–9). Prolonging inspiration does indeed raise mean airway pressure, yet we observed dramatically improved arterial oxygenation without adverse effect on $Paco_2$. The contrary would be expected if mean airway pressure were responsible for increased $\dot{V}/\dot{Q}$ mismatch.

The hemodynamic effects of prolonged inspiratory time cannot be fully quantitated from this case; however, we did not see a clinically relevant change in mean arterial pressure, pulse, or urine output. Other investigators (5) have reported that the increase in mean airway pressure observed with the technique we used in this case is not accompanied by changes in cardiac output or blood pressure (7,8). The effect on intracranial pressure was not measured. Some have suggested (10) that the higher mean airway pressures associated with a prolonged inspiration may lead to impaired cerebral venous return and worsening of intracranial hypertension. Stewart et al. (9), however, found no significant relation between prolonging inspiratory time and intracranial pressure.

In conclusion, although ventilation with prolonged inspiratory time has been superceded by other techniques, principally CPAP and IMV with PEEP, which have efficacy in diffuse disease, we propose that the use of prolonged inspiratory time is more effective in the presence of unilateral lung disease while avoiding the technical demands of double-lumen tube intubation and multiple ventilator circuits. Moreover, in cases in which sedation, paralysis, and repositioning are undesirable or impossible,

Table 1. Ventilator Settings and Arterial Blood Gases

Date	Time	FI_{O_2}	PEEP (cm H_2O)	f (breaths/min)	V_T (ml)	pH	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)	SAT (%)	Pao_2/FI_{O_2}	MAP (mm Hg)
10/5	01:00	0.4	5	14	700	7.36	29	51	—	128	77
10/5	02:00	0.8	5	14	700	7.44	30	69	95	86	81
10/6	11:15	0.5	8	6	700	7.44	38	62	91	124	83
10/6	12:00	0.5	12	6	700	7.44	38	54	88	108	83
10/6	16:00	0.5*	8	10	700	7.39	44	75	94	150	73
10/7	03:00	0.4*	8	12	900	7.46	32	70	—	175	88
10/7	22:00	0.4*	5	6	900	7.41	39	79	96	198	77
10/8	11:00	0.3*	5	4	900	7.42	40	74	93	247	83
10/8	19:00	0.3	5	CPAP	—	7.39	45	73	94	243	75

*Peak flow decreased from 60 to 40 L/min, waveform altered from constant to decelerating, end-inspiratory pause of 1 second, I:E, an abbreviation for inspiratory to expiratory time ratio; f, frequency—the number of breaths the ventilator delivers per minute; SAT, saturation of hemoglobin at the given arterial blood gas oxygen tension.

this technique offers the clinician another effective and easily implemented option.

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Letters to the Editor

Benzodiazepine Treatment of Penile Erection under General Anesthesia

To the Editor:

Stimuli that elicit penile erection are either psychic or reflex (1). Reflex erection, mediated primarily by the parasympathetic nervous system, depends on a spinal reflex arc that involves the second, third, and fourth sacral segments of the spinal cord. Psychogenic impulses, probably originating from the limbic system, phylogenetically the oldest part of the brain, coordinate sensory inputs with visceral function and emotion in humans; impulses descend via the lateral column of the spinal cord to reach the so-called thoraco-lumbar erection center at T12 and L1. Impulses at this center result in sympathetic stimulation that can act synergistically with the sacral parasympathetics to mediate erection.

Previous reports have shown that ketamine (2) or ketamine–physostigmine combination (3) can be used for the management of intraoperative priapism. Such therapy is based on the hypothesis that priapism is the result of reflex autonomic imbalance. However, subsequent studies (4,5) have questioned the efficacy of the ketamine–physostigmine combination.

We have found that the benzodiazepine derivatives, diazepam and midazolam, are effective in treatment of erection in patients undergoing surgery under general anesthesia. In six patients, erection was observed after induction of anesthesia, and occurred either spontaneously or secondary to penile manipulations during circumcision or cystoscopy. Erection was rapidly controlled by the intravenous administration of diazepam 5–20 mg in five patients, and by midazolam 10 mg in the sixth patient (Table 1).

Benzodiazepines exert multiple dose-dependent effects on the central nervous system. They act on stereospecific receptors in close proximity to the GABA receptors and probably potentiate the actions of the inhibitory neurotransmitter GABA at several sites in the CNS, including neurons in the cerebral cortex, substantia nigra, hippocampus, cerebellum, as well as the spinal cord (6,7). Also, it has been proposed that the central mechanism of action of benzodiazepines is inhibition of cellular uptake of adenosine and, thereby, enhancement of the central depressant effect of the nucleoside (8). Intravenous administration of benzodiazepines in the "spinal cat" increases dorsal root potentials, indicating enhanced presynaptic inhibition (9). Also, intrathecal administration of benzodiazepines has been shown to depress the nociceptive reflexes in the dog (10). The inhibitory effects of benzodiazepines at the spinal cord level may be responsible for inhibition of the erection reflex.

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Table 1. Summary of Patient Data

Age (yr)	Weight (kg)	Operation	Anesthesia	Dose of IV benzodiazepine
5	20	Cystoscopy and retrograde pyelography	Thiopental, N_20:O_2 and halothane	5 mg diazepam
8	30	Orchiopexy and inguinal herniorrhaphy	Thiopental, N_20:O_2 and alcuronium	2.5 mg diazepam
19	68	Hypospadius, uretheroplasty	Thiopental, N_20:O_2, fentanyl and alcuronium	5 mg diazepam
19	76	Circumcision and inguinal herniorrhaphy	Thiopental, N_20:O_2, fentanyl and alcuronium	20 mg diazepam
33	80	Circumcision and hydrocelectomy	Thiopental, N_20:O_2, fentanyl and alcuronium	10 mg diazepam
25	75	Circumcision	Thiopental, N_20:O_2, fentanyl and alcuronium	10 mg midazolam

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More on Long-Arm CVP Catheters

To the Editor:

I read with interest the Letter to the Editor, "Safe Placement of the Long-Arm CVP" (1) because we have been using this technique at our institution for several years. Expanding on this technique, when dealing with small children, we sometimes thread a 22-gauge Intracath catheter (Desert Medical, Inc.) through a 20-gauge Cathlon IVTM Catheter (Critikon). Unfortunately, this system does not work for the 19-gauge Intracath catheter. This catheter is too thin to pass through a 16-gauge Cathlon IVTM catheter without leaking and too large to pass through an 18-gauge Cathlon IVTM catheter. Perhaps someone knows of an IV catheter that will work as an introducer for the intermediate size 19-gauge Intracath catheter?

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Reference

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Determination of Halothane MAC in Swine

To the Editor:

Roberts et al. (1) recently reported that in swine the ratio between fatal and anesthetic concentrations (derived by dividing the fatal anesthetic concentration by MAC) for isoflurane was approximately double that of halothane. Because isoflurane and halothane MAC values were not determined by Roberts et al. (1), previously reported MAC values for swine were used as denominators in determining the fatal:anesthetic ratios (2,3). Roberts et al. (1) stated in the second paragraph of their discussion that, "Our calculation of safety margin depends on MAC. We used previously reported MAC values of 1.25% for halothane (2) and 1.45% for isoflurane (3). Tranquilli et al. (4), in contrast, reported a halothane MAC in pigs of 0.91%. This value was reported in much larger pigs (46–90 kg) than either we (32.6 ± 0.7 kg [SEM], range 24–39) or Weiskopf and Bogets (2) (24.7 ± 1 kg) used. Porcine weight correlates with age. The lower MAC values of Tranquilli et al. may reflect an older study group, as aging has been shown to lower MAC. Further, Tranquilli et al. (4) did not allow steady state equilibration for 15 minutes at each tested concentration; they instead assumed that a small alveolar to inspired difference indicated steady state. We believe the MAC of 1.25% determined by Weiskopf and Bogets (2) to be more relevant to our experiments and so chose to use it." Because the quantitative conclusions from the study by Roberts et al. (1) rely in part on the MAC values selected and, because our earlier studies of halothane MAC in swine (4) were considered and referenced in this paragraph, we are compelled to comment.

In defending their choice of the 1.25% halothane MAC value, Roberts et al. (1) unfortunately misconstrued the methods we used in determining the 0.91% halothane MAC value for swine. In the preceding paragraph, the second reason Roberts et al. gave for selecting 1.25% over the 0.91% halothane value as their comparison MAC was that, "Tranquilli et al. did not allow steady state equilibrium for 15 minutes at each tested concentration, but instead assumed that a small alveolar to inspired difference indicated steady state" (1). This statement is incorrect. First, in the Materials and Methods section of our report (4), we stated, "In each of the 12 pigs, halothane MAC was determined in standard fashion, using a large Kelly hemostat applied to the tail for 1 minute," and cite papers by Eger (5), Quasha et al. (6), and Eger et al. (7). In keeping with our understanding of standard methods, we used a period of at least 15 minutes of constant end-tidal halothane concentration at each concentration before the painful stimulus was applied. Second, we did not assume that small alveolar to inspired differences could be used in place of the 15 minute period of constant end-tidal halothane concentration. We reported our findings of small inspired to end-tidal halothane concentration differences but did not use these data to determine when our stimulus should be applied. The comments of Roberts et al. evidently result from misinterpretation of statements made within the discussion portion of our article with regard to the meaning of the ratio of inspired to end-tidal alveolar concentrations (4).

In the third paragraph of the discussion section of our article (4), we stated, "Alveolar (end expired) anesthetic concentration is a reasonable measure of brain anesthetic

dose if alveolar and arterial anesthetic partial pressures are similar and in a steady state. When alveolar anesthetic partial pressure-to-inspired anesthetic partial pressure difference is small, the potential error for an alveolar-to-arterial partial pressure gradient is decreased (8). Although the assumption that thermodynamic equilibrium exists between halothane in the alveoli and halothane in arterial blood has recently been scrutinized, that a steady state between alveolar and arterial partial pressures was near is indicated by the small inspired-to-alveolar (end-tidal) anesthetic difference (see Results)." These comments are in reference to the inspired and end-tidal halothane concentrations measured in our study, and have no relevance as to when stimulus was applied during determination of halothane MAC. Further, if we are correct in assuming that Roberts et al. concluded that we used inappropriate methods of MAC determination based on their interpretation of this paragraph in the discussion section of our article, they could have, at least, inquired further about our methods before also assuming we were unable to correctly organize our scientific publication under appropriate headings. Even when in doubt, the reader has a responsibility to respect the publishing authors, the publishing journal and its editors, and the institution of the scientific manuscript so as to abstain from extrapolating content of statements made in the discussion section of an article into methodology of data generation. That is the realm of materials and methods.

We also believe it is important to note that the MAC value for isoflurane quoted in the report by Roberts et al. was determined in a closely allied laboratory in the College of Veterinary Medicine, University of Illinois, using the same standard techniques for MAC determination that we used (3). Finally, some of our more recent experiences may be of additional interest. In a recent, as yet unreported study at the University of California at Davis (EPS), halothane and isoflurane MAC values were determined in seven Hormel strain miniature swine (1.3 ± 0.2 [$\bar{X}$ ± SE] years of age; 86.5 ± 2.4 kg). Studies on a given animal were separated by at least 2 weeks. The results were: halothane MAC = 0.90 ± 0.06% (at 38.3 ± 0.3°C; n = 7); isoflurane MAC = 1.49 ± 0.04% (at 38.7°C; n = 6). In another previously published study using domestic swine (2.5 to 3.5 months of age when the study began) of several breeds (i.e., Hampshire, Yorkshire, Landrace, and Duroc), halothane (n = 9) and isoflurane (n = 7) MAC values were determined to be 0.94 ± 0.03 and 1.75 ± 0.1%, respectively (9). More recently, in a separate group of 3- to 4-month-old hybrid pigs (Yorkshire, Chester White, Landrace crosses), we again similarly determined the MAC value for isoflurane to be 1.56 ± 0.07% (n = 6) (10).

In conclusion, it is not our intent to be harshly critical of the investigation by Roberts et al. Indeed, we find their study interesting and informative and believe their results offer additional justification for the contemporary popularity of isoflurane. However, we feel compelled to comment on the misinterpretation of our previously reported methods. Although the 1.25% MAC value may have been more appropriate for the study by Roberts et al. because of the age and size of their pigs, it is not more valid than the 0.91% MAC value because of time allowed for equilibration at a given end-tidal halothane concentration. The time allowed for steady-state equilibration at a given end-tidal halothane concentration was at least 15 minutes in both studies.

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In Response:

Tranquilli et al. are upset about the fact that, when calculating the ratio between fatal and anesthetic concentrations, we chose the previously published 1.25% MAC value for halothane in pigs rather than their 0.91% value for halothane in the same animal. We believe we had good reason for using the 1.25% level, and continue to believe so for the reasons stated in our paper and in their letter. We regret that we may have misinterpreted their methods section as indicating that they did not achieve a full 15-minute end-tidal equilibration at each concentration level. Nonetheless, our reasons for choosing the 1.25% MAC level still seem valid to us. Also, of course, we cited their work and therefore any reader is free to substitute their 0.91% MAC level for halothane for the 1.25% value we used in our

calculations. We do not believe that would change our conclusions at all. We would like to point out that the discrepancy in the determinations of MAC values for this animal may indicate that a "standard," i.e. tail clamp, determination of MAC may be more difficult to do in pigs than in dogs, perhaps because pigs do not have particularly well developed tails, or for some other reason. If the pig is to become a much more commonly used experimental animal, and we believe that it will be for many reasons, then the problem of determining MAC in this species must be thoughtfully addressed in the future. We thank Tranquilli et al. for their comments regarding our paper.

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Preoxygenating the Anxious Patient

To the Editor:

Despite the opinion of Gaines and Rees (1) that preoxygenation upsets anxious patients too much, and despite the anxieties of psychiatric as well as many other patients, including pediatric patients, we agree with Riley (2) that the safety margin provided by preoxygenation should not be sacrificed even in anxious patients. A denitrogenated functional residual capacity (FRC) can buy precious minutes when airway problems unexpectedly arise. We have used a preoxygenation technique that is readily accepted by psychiatric, anxious, or pediatric patients who are frightened by the anesthesia face mask.

When asked, almost all of these patients are cooperative and place a plastic elbow attached to an anesthetic circuit in their mouth and breathe 100% oxygen. In fact, many will hold the circuit with one hand while holding their nose closed with the other. This patient participation seems to noticeably reduce anxiety.

Alternatively, with a little time for preparation, a disposable plastic mouthpiece (available from a respiratory therapist) can be adapted to the anesthetic circuit so that the patient can breathe through it during the preoxygenation. Measurements of arterial blood gas tensions confirm the efficacy of this technique in several patients with arterial catheters in place (Table 1). The technique can also be used in patients with abnormal facial anatomy due to burns, previous surgery, etc., which precludes a satisfactory mask fit. With the above technique added to the usual methods, it is the rare patient who cannot be adequately preoxygenated.

Table 1. Pao_2 Data*

	Room air	After 1 min preoxygenation
Pao_2 (mm Hg)	86.9 ± 7.3	297.1 ± 85.0

*Values are mean ± SD.
$N = 7$. (unpublished data).

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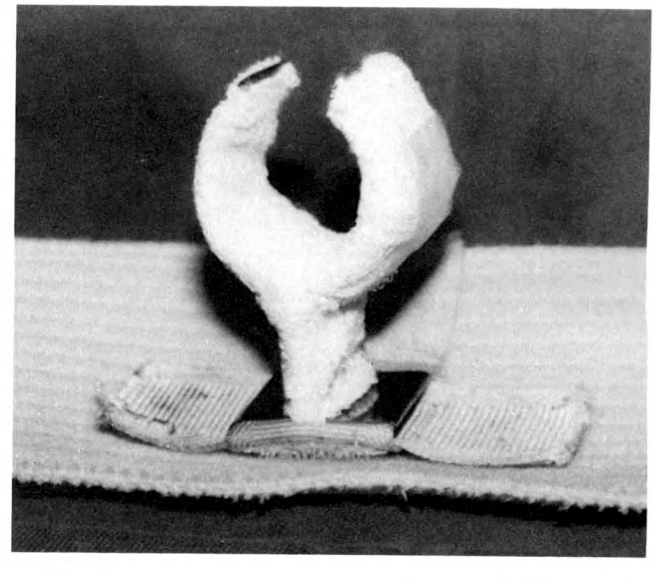
Modification of Anesthesia Circuit Tube Support Strap

To the Editor:

During maxillofacial surgery with nasotracheal intubation, the anesthesia circuit tube must be fixed securely to prevent disconnection caused by movement of the patient's head by the surgeon. Sawhney and North have described an easy to use, commercially available support strap (1). Circuit tube holders are located directly on the headband of these straps, making it necessary to use an acute angle connector between the nasotracheal and anesthesia circuit tubes to avoid pressure on the nares (2). However, this acute angle makes endotracheal suction difficult and increases flow resistance. Moreover, the anesthesia circuit tube tends to hang down, which may either aggravate the pressure on the nose or result in disconnection. We have solved these

Figure 1. Removable tube holder with Velcro base for attachment to Sawhney's support strap (1).



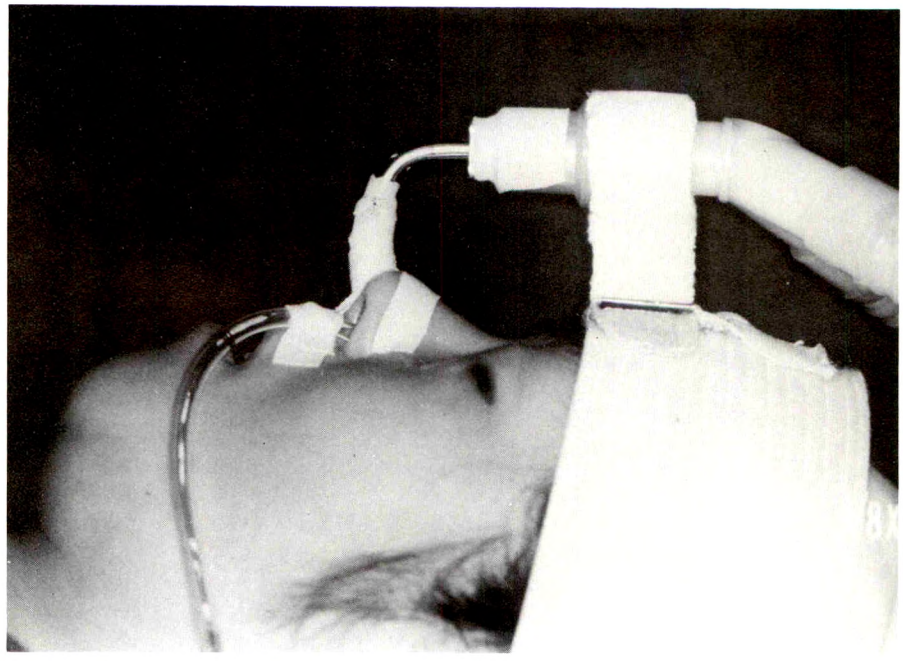


Figure 2. Side view of modified anesthesia circuit tube holder.

problems by using the tube holder shown in Figures 1 and 2. This holder is attached with Velcro and does not interfere with induction or extubation. Besides, the holder can be used not only for circle systems but also for Bain and other circuits. We have used this equipment in over 30 patients and have found good stability of the circuit tube and reduced pressure on the patient's nose.

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Relative Risks of Epidural Air Injection in Children and Adults

To the Editor:

Identification of the epidural space can be accomplished by a loss-of-resistance (LOR) technique using fluid or air. Dalens, Bazin and Haberer (1) recently reported two cases in which the epidural injection of air for LOR testing was associated with incomplete analgesia in young children (weighing 18.5 and 19.5 kg). Unanesthetized areas developed at the segmental levels where epidural air bubbles were seen on peridurograms. The authors conclude by cautioning against the use of air for loss of resistance, stating that risks with other LOR identification techniques are "minor when compared with the risk of incomplete analgesia." This relative risk analysis warrants further discussion.

The first issue relates to the risk of incomplete analgesia. In another study involving 132 parturients (2), the epidural space was identified by a loss of resistance using 2 ml air; 63 of the women received an additional 10 ml epidural air injection (as part of an evaluation of catheter complications). All 132 adult patients developed satisfactory anesthesia, with no segmental defects. The differing results between the studies may well be related to the different patient populations—children and adults. Dalens et al. (1) comment on the anatomic difference. In children, the epidural space extends along the spinal nerves, which may facilitate bubble trapping. I would add to that the relative difference in volumes: the volume of air injected compared to the smaller volume of the epidural space in children rather than adults.

The second issue relates to the relative risk of other LOR techniques that can be used to identify the epidural space. The injection of up to 10 ml of local anesthetic drug has been used (3), but this carries the danger of total spinal anesthesia or intravascular toxic reaction. The epidural injection of distilled water causes burning pain (4) and, therefore, should not be used in the unanesthetized patient. Preservative-free normal saline injection has been

suggested as safe, but with the potential to dilute the drug and thereby jeopardize anesthetic result (1); this hypothesis remains to be studied.

Therefore, on one side of the risk balance, each of the other agents that can be used for LOR testing does carry the potential for specific complications. On the other side of the balance, segmental defects in analgesia secondary to epidural air injection are not common in adults, as demonstrated by 2–12 ml given to 132 women. The use of air to test for epidural space entry does, of course, have potential hazards of its own, including vascular air embolism and subcutaneous emphysema (2). Weighing these factors, I suggest that the loss-of-resistance technique using small volumes of air, injected with caution, remains a good risk for identifying the epidural space in the adult patient.

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Right Bundle Branch Block during Insertion of an Intravenous Guidewire

To the Editor:

Intravenous guidewire insertion before pulmonary artery catheter placement may cause a high incidence of atrial and ventricular arrhythmias (1). We report the following case of ventricular arrhythmias and right bundle branch block precipitated by guidewire insertion.

A 30-year-old male with paraplegia at a level of T12 was scheduled for repair of a bulbo-urethral fistula. Venous access was difficult and the patient was eventually anesthetized using a 22-gauge peripheral intravenous catheter. Additional venous access, however, was needed. The right internal jugular vein was cannulated without difficulty and an intravenous guidewire (floppy end) was placed prior to insertion of a central venous pressure (CVP) catheter. During guidewire insertion numerous premature ventricular contractions were seen on the ECG monitor and the wire was withdrawn several centimeters with disappearance of the arrhythmias. However, the QRS complexes, previously narrow, were now wide. The double-lumen CVP catheter was inserted uneventfully.

An intraoperative 12-lead ECG compared to his preoperative ECG now showed a right bundle branch block pattern

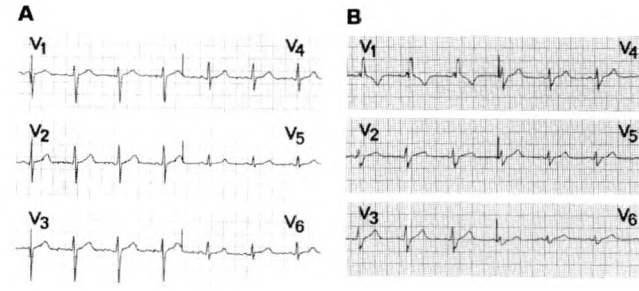

Figure 1. (**A**), Preoperative ECG showing the precordial leads V_1–V_6 (normal pattern). (**B**), Intraoperative ECG of V_1–V_6 after intravenous guidewire removal revealing a new right bundle branch block which spontaneously resolved 2 hours later.

(Fig. 1). There was no history or physical evidence of previous cardiac disease. The patient remained hemodynamically stable and the surgery and anesthesia proceeded without problems. Two hours into the case, the QRS complexes returned to a narrow pattern. The operation was completed and in the recovery room the ECG was identical to that obtained preoperatively.

Right bundle branch block can occur during insertion of pulmonary artery catheters and may cause complete heart block in the presence of a preexisting left bundle branch block. The guidewire is sufficiently long to easily enter the right ventricle when inserted too far. Most guidewires require insertion of only one-half of their length to guide catheters into the venous system and allow proximal control of the wire. This is, to our knowledge, the first case reported of an intravenous guidewire causing a right bundle branch block. Physicians should be aware of problems with arrhythmias and right bundle branch block when using the Seldinger technique for insertion of central catheters.

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3-in-1 Block: Confirmation of Winnie's Anatomical Hypothesis

To the Editor:

In 1973 Winnie et al. (1) described a technique for blocking the femoral, obturator and lateral femoral cutaneous nerves with a single injection of local anesthetic solution, the 3-in-1 block. The anatomical basis for the block was Winnie's description of a plane between quadratus lumborum and

psoas major in which all three nerves run. Local anesthetic solution introduced into this plane will spread the block to all three nerves. His initial description involved injecting local anesthetic around the femoral nerve (1).

In 1980 Sharrock described unintentional 3-in-1 block after injection of the lateral cutaneous nerve of the thigh (2). The present report describes a similar case confirming Sharrock's observation and thereby demonstrating the validity of Winnie's observation.

The patient was a 29-year-old man who presented to the pain clinic with a diagnosis of meralgia parasthetica. The right lateral femoral cutaneous nerve of thigh was blocked where it lies deep to fascia lata inferomedially to the anterior superior iliac spine, using a 23-g, 25-mm needle and 10 ml 0.5% bupivacaine mixed with 10 mg methylprednisolone. Parasthesia was not sought. Shortly afterwards sensory loss developed in the L2/3 distribution, followed by increasing weakness of hip flexion, knee extension, and adduction of the thigh indicating blockade of the femoral and obturator nerves. This lasted for several hours.

It seems likely that the local anesthetic solution injected spread cephalad to reach the plane between quadratus lumborum and psoas major, blocking the lumbar plexus. This confirms Winnie's original hypothesis that blockade of the femoral, obturator and lateral femoral cutaneous nerves can be achieved by introducing local anesthetic solution into this anatomical plane (1).

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Endotracheal Intubation in Temporomandibular Ankylosis

To the Editor:

I wish to express concern regarding the report by Baraka (Anesth Analg 1986;65:1089–92) describing a method for the introduction of an endotracheal tube into a 17-year-old girl afflicted by temporomandibular ankylosis.

First, he does not, in my opinion, satisfactorily explain or justify the choice of his specific technique for this particular patient and he makes no mention of simpler, safer ways being tried, and failing, beforehand.

Surely anesthesiologists confronted with "difficult intubations" should always try the simplest, safest methods initially and then, only if failure occurs with these, should progressively more complicated or more invasive techniques be used. These latter, it is hoped, not being regarded and utilized as substitutes for experience, practise, or the proper acquisition of appropriate skills. Unless an orderly, planned, sequential approach is employed toward the intubation and the anesthesia, it becomes difficult to explain or defend the occurrence of serious complications, rare though they may be, such as can be associated with crico-thyroid puncture (1–6).

Second, the terms "difficult intubation" and "difficult airway" are used as if they are synonymous or interchangeable. However they are not always, nor are they even necessarily associated. Moreover the mere presence of temporomandibular ankylosis does not signify, in my experience, either a "difficult airway" or a "difficult intubation" unless there are other features also present. These may include, for example, micrognathia, limited atlanto-occipital or neck movement, obstructive pathology in the upper airways, severe tissue edema, fibrosis or scarring, or morbid obesity, etc.

I have successfully performed blind nasal intubations on over 300 patients troubled by temporomandibular ankylosis or gross trismus, during the last 11 years, without use of a fiberoptic laryngoscope, transtracheal ventilation, retrograde catheterization, light wand, or tracheostomy. The ages ranged from 2 years to 72 years and body weight from 9 kg through 124 kg. I adhere to the maxium "let the anesthesiologist look after the airway and the intubation look after itself." I hope that the intubation will be straightforward and take only a few seconds but I am unable to distinguish beforehand those which will take longer, i.e., those that will take 5 or 30 or even 50 minutes. It is for this reason that I believe that "difficult intubation" should be a retrospective and not a prospective diagnosis or assessment.

On the other hand, features affecting the airway can and must be carefully assessed beforehand because they concern the patient's safety and determine the approach to be used and the form of anesthesia. Although many avoid the issue and employ topical anesthesia, I prefer to use a thiopental-succinylcholine induction sequence as often as possible. When I am unsure of the airway I will fall back on an inhalation induction anesthesia and only if I judge the airway unsafe will I utilize sedation and/or topical anesthesia. Experience is useful, even vital, in making such decisions and may be taxed to the limit. If I fail on the first attempts at blind nasal intubation I make the next attempts with the endotracheal tube curved to an appropriate shape with an ordinary malleable metal stylet. When I fail in the paralyzed apneic patient I convert to a spontaneously breathing inhalation anesthetic and try intubation again without, and then if necessary with, the aid of the stylet to curve the tube. It was this sequence that was successful in a 124-kg short-necked individual suffering from gross trismus due to dental infection and, to date, I have not had to proceed further along my planned scheme. The stylet has been required only infrequently.

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In Response:

Thank you for referring to me the comments of Dr. Williamson concerning my Letter to the Editor, "Transtracheal Jet Ventilation During Fiberoptic Intubation Under General Anesthesia" (1).

I agree with Dr. Williamson that "difficult intubation" and "difficult airway" are not synonymous, although the two conditions may occasionally coexist in the same patient. Also, I agree that simple maneuvers such as blind nasotracheal intubation may be initially attempted in such cases. Unfortunately, blind nasotracheal intubation is becoming a "lost art" among the new generation of anesthesiologists (2), who have moved to fiberoptic laryngoscopic intubation under local or general anesthesia.

The main goal of our report is not to recommend TJV and/or fiberoptic laryngoscopic intubation, but simply to illustrate the use of TJV as a method of ventilation in patients undergoing fiberoptic intubation under general anesthesia. TJV may be advantageous and even life-saving in patients having "difficult airway" associated with "difficult intubation" (3).

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Rapid Induction of Anesthesia with Isoflurane

To the Editor:

I would like to comment on the paper by Loper et al. (1) comparing a single vital capacity breath (VCB) induction of anesthesia using halothane or isoflurane. We recently reported on a similar technique, but there are important differences between the two studies (2). Our aim was to demonstrate that isoflurane was acceptable to patients, even though the pungent odor suggested it might not be. Loper et al. wished to demonstrate that isoflurane was more rapid than halothane for VCB induction of anesthesia. We had assumed this to be the case from the physical characteristics. We accepted that halothane has been successfully used with this technique, and therefore chose to compare a VCB induction of anesthesia with a conventional multi-breath one (3,4). We studied unpremedicated patients, as would be the usual situation in day-case surgery.

We were surprised that Loper et al. used what we considered to be a large dose of fentanyl (5 μg/kg), and were even more surprised that their patients breathed at all afterwards!

The final difference was that we used isoflurane in nitrous oxide to deliberately reduce the concentration of isoflurane vapor required. It is of interest that despite these differences between the studies the results were similar. Both reports have a mean number of two breaths before the onset of unconsciousness or amnesia. Both studies show a small reduction of mean arterial pressure with a VCB of isoflurane. Patient acceptability in our study was 94% and in that of Loper et al., it was complete. We further demonstrated that a VCB of isoflurane is more acceptable than a conventional inhalation induction.

Loper et al. used fentanyl to suppress the cough reflex. This would seem to be unduly pessimistic as our study showed coughing to only rarely be a problem with a VCB of isoflurane.

In conclusion, both studies confirm that a single vital capacity breath induction of anesthesia using isoflurane is a valid and new addition to our armamentarium and the decline in the use of halothane may make it increasingly useful.

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Automatic Blood Pressure Machine Revisited

To the Editor:

Noninvasive automatic blood pressure sphygmomanometry (1) has become a common and useful component of clinical anesthesia today, but its disadvantage is the long

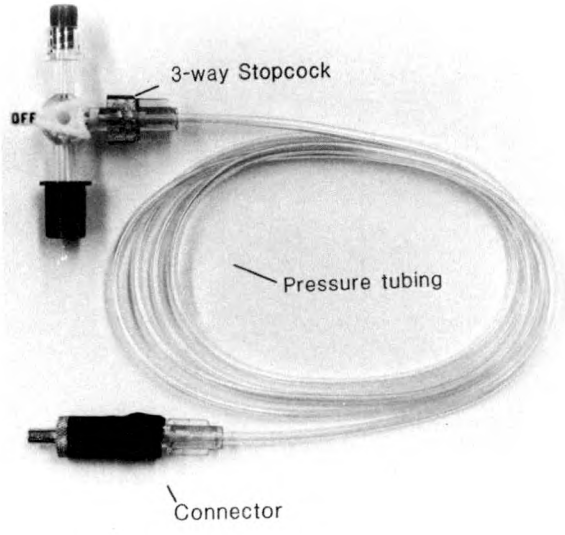

Figure 1. As text describes, three-way stopcock is connected to the automatic blood pressure machine. The "connector" end is inserted into the anesthesia machine.

time from the start of its automatic cycle to final blood pressure determination. This can seem like an eternity in times of emergency or rapidly changing clinical conditions. Some manufacturers have foreseen this shortcoming and have installed a "STAT" cycle on their product to enable quicker results. Even this feature is inadequate at times.

I would like to share an innovation that should make my colleagues' life better in the operating suite during times as described above when it would be advantageous to have a ballpark estimation of blood pressure *prior* to the automatic blood pressure machine's determination.

A simple modification can be implemented using commonly found material in the operating suite. Needed equipment include:

–pressure extension tubing
–luer lock three-way stopcock
–assorted adapters (male/female)
–short rubber tubing,

which should be assembled as shown in Figure 1.

After positioning the lever of the three-way stopcock so that the stopcock is open in all directions, disconnect the tube running from the blood pressure cuff to the automatic blood pressure machine. Connect one end of the stopcock to the blood pressure machine, another end to the tubing that goes to the blood pressure cuff, and the third arm (via the pressure tubing) to any standard blood pressure gauge (commonly one is already a part of most anesthesia machines).

This arrangement permits the automatic blood pressure machine to continue its standard cycle of inflation and deflation while simultaneously causing the needle on the standard blood pressure gauge to rise and fall. As the automatic cuff pressure decreases, the magnitude of the oscillations on the standard manometer should suddenly increase when the systolic blood pressure is reached and arterial flow begins beneath the cuff (applying the principle of oscillometry). When the diastolic blood pressure is reached the oscillations abruptly decrease.

When one would like to "know" what the blood pressure is *prior* to the automatic blood pressure machine's final calculation, the above modification will allow the anesthesiologist to get a ballpark estimation that may assist in further clinical decision-making processes.

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Reference

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Should Calcium Administration Be Avoided in Treatment of Hyperkalemia in Malignant Hyperthermia?

To the Editor:

The lack of direct evidence notwithstanding, it has been suggested that calcium administration may cause or worsen malignant hyperthermia (1,2). We describe a patient in whom cardiac arrest occurred as a result of hyperkalemia during an episode of malignant hyperthermia. The patient was successfully treated with dantrolene plus calcium gluconate, the latter being given in the course of resuscitation from cardiac arrest.

The patient was 13-year-old boy scheduled for the removal of a fibular tumor. Preoperative physical and laboratory examinations were normal. Anesthesia was induced with thiopental followed by halothane (1–3%) and oxygen. Five minutes after induction, muscle rigidity of the abdomen and the lower extremities was noted and a multifocal ventricular arrhythmia developed. The patient, easily intubated without use of a muscle relaxant, was ventilated with oxygen and the halothane was discontinued. At this time, the rectal temperature was 38.6°C and an arterial blood sample showed pH to be 6.86, $Paco_2$ 120 mm Hg, Pao_2 522 mm Hg, and base excess −16.6 mEq/L; serum potassium was 6.9 mEq/L. The diagnosis of malignant hyperthermia was made and body cooling by alcohol sponge, intragastric lavage with cooled saline and intravenous infusion of cooled lactated Ringer's solution were initiated. Dantrolene, sodium bicarbonate, regular insulin, and furosemide were administered intravenously. Within 40 min of induction, the metabolic and respiratory acidosis were corrected and the temperature, having reached a peak of 39.9°C, began to decrease. However, the serum potassium level further increased to 7.4 mEq/L, and profound brady-

cardia followed by cardiac arrest developed. Cardiac massage was started and, shortly after the administration of 25 ml of 8.5% calcium gluconate, a sinus rhythm was restored. No further arrhythmias occurred and the serum potassium level decreased to normal level in 2 hours. During subsequent hours, the muscle rigidity gradually subsided and the patient made a satisfactory recovery.

It is well known that malignant hyperthermia may be associated with severe hyperkalemia causing arrhythmia and/or cardiac arrest (3). The most rapid and effective method of dealing with hyperkalemia in malignant hyperthermia has been considered to be a correction of blood pH by the administration of sodium bicarbonate (4). However, in our case, serum potassium levels increased and were followed by cardiac arrest even after correction of the metabolic and respiratory acidosis. Calcium gluconate promptly reversed the cardiac arrest without causing further aggravation of malignant hyperthermia symptoms. Recently, Gronert et al. (5) reported that calcium does not induce malignant hyperthermia in the susceptible swine. We think that calcium can and should be given when potassium levels achieve cardiotoxic values during a malignant hyperthermia episode, though, of course, the mainstay for the treatment remains the administration of dantrolene.

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Retrograde Intubation with a Modified Eschmann Stylet

To the Editor:

The failure to intubate a patient at the beginning of a planned "routine" general anesthetic is one of the most challenging and potentially dangerous events in clinical anesthesia. During a recent confrontation with this problem, we modified some standard intubating aids and developed a new approach to intubating the difficult airway.

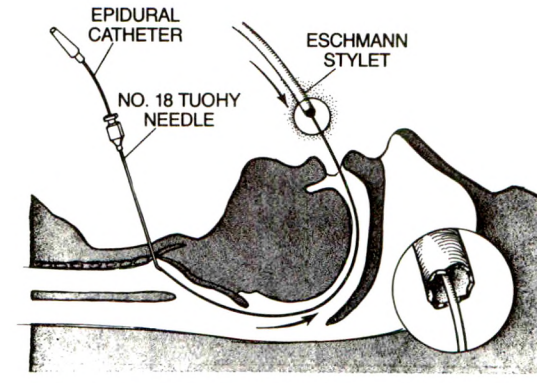

Figure 1. Cross-sectional view of Tuohy needle placed through cricothyroid membrane and retrograde passage of epidural catheter through glottis and exiting via the mouth. Modified Eschmann stylet is then passed over the epidural catheter through the oropharynx and glottis into the trachea. Insert: Cut end of Eschmann stylet so that epidural catheter can be passed through the stylet.

Our patient, a 57-year-old, 85-kg man was scheduled for an elective lumbar laminectomy for correction of his spinal stenosis. Except for progressive lower extremity weakness, past medical history, laboratory values, and physical examination were unremarkable. After routine monitors were applied (including a pulse oximeter), anesthesia was induced with thiopental (4 mg/kg) and fentanyl (100 μg), and muscle relaxation was facilitated by 12 mg pancuronium given in divided doses over 5 minutes. After all attempts at intubation with a variety of laryngoscopes, endotracheal tubes, and an Eschmann stylet were unsuccessful, an epidural catheter was passed retrogradely through an 18-gauge Tuohy needle via the cricothyroid membrane into the oropharynx. We then attempted to pass the endotracheal tube over the epidural catheter but the catheter was not rigid enough and the endotracheal tube would not pass anteriorly through the larynx. In an attempt to make the epidural catheter more rigid, we decided to pass the Eschmann stylet (Fig.1) over the epidural catheter. The woven ends of the stylet were cut (see insert Fig. 1) so that the stylet could be easily passed over the epidural catheter. The two cut ends of the Eschmann stylet were smoothed so that the oropharynx and trachea would not be injured. The Eschmann stylet easily passed into the trachea and then the epidural catheter was withdrawn through the cricothyroid membrane. The endotracheal tube was then passed over the Eschmann stylet into the trachea. Once the trachea was intubated, the case proceeded uneventfully, including extubation.

The logical approach to the "failed intubation" has been reviewed in depth recently (1). The routine approaches should be applied first and only in a last attempt should an esoteric method as described here be attempted.

It would be helpful if the Eschmann stylet could be manufactured with open ends. This would facilitate the passage of a guidewire or catheter through the stylet and allow the aspiration of gas (CO_2) to confirm the intratra-

cheal position of the stylet tip or serve as a means for insufflation of oxygen into the trachea.

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Reference

1. Holmgreen WC, Nishioka GJ. Difficult intubation: unsuspected. In: Bready LL, Smith RB, eds. Decision making in anesthesiology. Philadelphia: BC Decker, 1987:18–9.

Book Reviews

The History of Blood Gases, Acids and Bases

Poul Astrup, John W. Severinghaus. Munksgaard International Publishers, Copenhagen: 1987, 331 pp, $34.95.

Readers expecting to find textbook-like reference material and detailed technical information on blood gases, acids and base physiology will be disappointed in this book. However, if the goal is to browse through an enjoyable look at the people and events that formed the basis of our modern understanding of this subject, this is the right vehicle. The book is organized into two major sections, each written by a different author. The first and longest section (263 pages, chapters 1–17) is written by Poul Astrup, and covers the progress of mankind in understanding blood gases and acid-base physiology from the earliest writings (*circa* 4000 BC) up to the modern era, arbitrarily set at 1950. The second section, written by John Severinghaus, consists of one chapter (33 pages) and reviews the advances in measurement technology from 1950 up to approximately 1985.

The two sections are written in very different styles. Dr. Astrup's section reads like a light and airy series of brief biographic and historic vignettes, each dealing with a specific event, person, or milestone in the progress of mankind toward understanding of blood gas science. It is enjoyable and amusing for the modern reader to follow the development of understanding through the ages from the privileged prospective of an initiate into the "truth." (One wonders if readers of a parallel work in the future will be similarly amused by our present level of understanding.) Dr. Severinghaus's chapter reads much like an entry in the personal diary of a man who has seen and participated in the events chronicled therein as, indeed, he has.

The book begins with Astrup's section and the earliest beliefs of the Greek philosophers Empedocles, Anaximenes, and Diogenes, in the four fundamental elements of Nature—earth, water, air and fire. Our early professional colleague, *Hippocrates*, expanded this concept to include the four humours: blood, phlegm, black bile and yellow bile, while Aristotle taught that the arteries carried air, and the veins, blood, to the periphery of the body. According to Aristotle's teaching, the lungs served to cool the blood and to supply it with air. From this auspicious beginning, Dr. Astrup guides the reader through the slow and often painful progress associated with scientific advancement. One epoch that I found particularly interesting dealt with the development of and experiments with a vacuum pump, this because I remember working with one as a high school student in science class. It seems that one Otto von Guericke (1602–1686) was exploring ways of making wooden barrels airtight, and in the process he invented the vacuum pump and discovered the enormous forces that air pressure was capable of exerting. Von Guericke built two hemispheres that fitted each other so tightly that it was impossible for air to enter into them once they had been pressed together and the air trapped between them had been pumped out. Once the assembly had been formed, sixteen horses were unable to draw them apart. But if air was admitted to the vacuum chamber by opening a small valve, even a small child could separate the two hemispheres. Such dramatic demonstrations of science in everyday life had a profound impact on society. People were astounded at the enormous forces the existence of which nobody had suspected. Because the existence of vacuum was at variance with the ancient Greek beliefs, von Guericke's experiments touched off a major debate in Europe among philosophers intent on proving it in error. Much the same thing happens today with the announcement of a new discovery that casts doubt on old and often cherished beliefs.

Astrup continues with his exposition of the discovery of air and air pressure. He details the confused and jumbled elaboration of the phlogiston theory to explain the phenomenon that occurs when combustion occurs in a closed vessel. He takes the reader through the discovery of the gas *oxygen* and the later discovery of "fixed air" or *carbon dioxide*. He then tracks the development of theories of acid and base metabolism. Along the way, he explains and illustrates much of the often confusing nomenclature associated with acid-base physiology.

Near the end of Astrup's section, he begins to detail some of the modern technology such as the *Van Slyke* apparatus that played a critical role in modern measurement technology. His last chapter deals with the events leading to the development of modern intensive care units, the polio epidemic in Copenhagen in 1952–1953.

At this point in the narrative, Dr. Severinghaus takes over with his chapter entitled "AHA!." "AHA!," according to Dr. Severinghaus, ". . . is a millisecond event during which two unconnected thoughts connect—in a new and creative way." To illustrate his point and to serve as a paradigm for a description of our "advanced science" of blood gas technology, Dr. Severinghaus offers Piet Hein's grook called "Our Noblest Achievement":

> "We must expect posterity
> to view with some asperity
> the marvels and the wonders
> we're passing on to it;

but it should change its attitude
to one of heartfelt gratitude
when thinking of the blunders
we didn't quite commit."

Severinghaus then goes on to state the secret of his and other's success in exploiting the AHA! method of scientific advance: ". . . In being creative, the trick is to be both involved enough to be full of ideas, and uninvolved enough to let them tumble around until they snap together in a new way—**AHA!**" Good advice . . .

Dr. Severinghaus then goes on to chronicle the events leading to the three great new ideas, AHA!s, that brought about modern blood gas analysis. They were:

1. Poul Astrup's measurement of pH and Pco_2 with a single pH electrode,
2. Richard Stow's invention of a CO_2 electrode using a gas permeable membrane, and
3. Leland Clark's platinum Po_2 electrode behind a polyethylene membrane.

He covers each great AHA! in detail, written from the perspective of the insider that he was and is. As I was reading this chapter, I began to resolve in my own mind some of the confusion that I had accumulated over the years in the field of blood gas measurement technology. I was delighted with the clear and direct descriptions that are the Severinghaus trademark.

In summary, this is a good book, clear and well written. It is not a textbook or reference work, but rather a narrative, often entertaining, always interesting, of the advances leading to the modern understanding of blood gases, acids and bases.

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Blood Transfusion Therapy, a Physician's Handbook, Second edition

Snyder EL, ed. Arlington, Virginia: American Association of Blood Banks, 1987, 94 pp, $3.50.

Blood Transfusion Therapy, an Audiovisual Program

Kennedy MS, Snyder EL, eds. 77 slides, 75-page manual, and one tape, $165.00.

The second edition of Blood Transfusion Therapy is a summary of the current practice of transfusion medicine. Nevertheless, the 94 pages contain sufficient information that rarely will one need to refer to the 98 references cited. The AABB's Component Therapy Committee prepared this second edition just 4 years after the first edition, a period of considerable change. For example, Consensus Development Conferences (CDC) on FFP and platelets have been held in the interim and the recommendations of those CDCs are reflected in the text. The four sections, blood components, transfusion practices, hemostatic disorders, and transfusion reactions cover all common areas of transfusion medicine as well as some of the more rare entities. The format, a small ($4\frac{1}{2}$" × $7\frac{1}{2}$") paperback, readily fits into the jacket pocket and could be accessible in the O.R. for it would not take up much room on the anesthesia machine. In this reviewer's opinion this small manual remains the best concise summary of current transfusion medicine and is recommended highly to anyone who must decide when and what blood product to administer to a patient.

In combination with the other four parts of the Transfusion Medicine Self-Assessment Program series (Data Card, Self-Assessment Examination, Audiovisual Slide Program, and Patient Management Problems), a concise summary of transfusion medicine is transferred into a lesson plan that can be of extreme value to students and instructors alike. Data cards could readily be available in every O.R. for quick reference, whereas the self-assessment exam and the clinical management problems lend themselves to self-instruction in the way that the ASA's popular self-assessment program does. The audiovisual program is a splendid supplement for those who are in a position to teach various aspects of transfusion medicine and can be used as a complete teaching unit or as a supplement to material that may be more specific to anesthesia.

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Applied Respiratory Physiology Third Edition

J. F. Nunn. England: Butterworth, 1987, 587 pp, $54.95.

When I first began my formal research training, a mentor advised me to read John Nunn's Applied Respiratory Physiology to see how physiology can be made relevant to the practice of anesthesiology and intensive care. I followed that advice and have on my bookshelf that first edition, published in 1969, the second edition, published in 1977 and, now, Dr. Nunn's third edition. The book reflects the impressive achievement of a single-authored book covering topics in sufficient detail to reflect both what is known and, as important, what is not known. The book fulfills the author's stated purpose of presenting general principles of respiratory physiology, concentrating on those relevant to anesthesiology with a solid selection of appropriate citations. The goal of offering physiologic mechanisms as a basis for formulating clinical practice as an active intellectual pursuit rather than the ritual of few simplistic paragraphs on "physiology" before a detailed clinical "cookbook" is to be applauded. The book continues to fill this need.

Chapters on anatomy, respiratory mechanics, ventilation-perfusion relationships, gas transport, and control of breathing are all excellent presentations of basic physiology with explicit linkage to anesthesiology usually missing in other physiology texts. Five chapters on oxygen and carbon

dioxide, their physical properties, and physiologic effects provide a wealth of information.

The third edition differs from the prior editions in offering a separate section of 17 chapters in which the basic physiologic principles are applied to specific clinical problems. The results are highly variable. Some of these chapters are superb and link with the earlier chapters, reflecting Dr. Nunn's major interests. The chapter on "Respiratory Aspects of Anesthesia" should be read and understood by every anesthesiologist. A number of chapters are basic primers that will start a novice on the right track to learn more. This is particularly true in those chapters in which recent reviews are cited to facilitate the task. A few chapters (e.g., on neonates and children; drowning; pulmonary embolism; smoking) are weak and could probably be omitted to preserve the otherwise high quality of this book.

The breadth of Dr. Nunn's knowledge and his ability to communicate the vitality of his subject has stood the test of time. This book is reasonably priced. It should be purchased by those individuals interested in classical organ-level respiratory physiology and by all departmental libraries. It should be read by residents and anesthesiologists who want to think before ventilating.

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Cardiovascular Anesthesia, Vol. 1, No. 3 in Problems in Anesthesia Series

S. T. Thomas, ed. Philadelphia: JB Lippincott, 1987, 194 pp, $25.00.

This, the third volume in The Problems in Anesthesia series, deals with topics related to cardiovascular anesthesia. It is quite accurately portrayed in the forward as ". . . a potpourri of subjects . . ." and, indeed, the topics are not cohesively related. This fragmentation is assisted by a loose editorial hand, resulting in a range of approaches from the parochial, familiar, empirical "how we do it here," to an objective comprehensive display of knowledge in a well focused area. The latter, of course, represents a few chapters that the editor suggests ". . . will serve as a ready summary. . . ." The former are interesting, informative, and probably one-time reading. Thus, the volume does have ". . . something for everyone."

There are 11 chapters, 3 of which focus on ischemic heart disease. Some repositioning of chapter sequence and more editorial involvement to reduce repetitive material would have improved this area. However, each could stand alone. The first of these, by London and Mangano, provides an excellent review and analysis of the assessment of perioperative risk. It should be read by internists and surgeons as well as anesthesiologists. The other two chapters by McIntyre and Reeves and Harrison and Levin add supportive material on management and pathophysiology of ischemic heart disease.

Controversy is nicely displayed for the reader by Thomsen in neurological aspects of cardiopulmonary bypass and equally well by Lubarsky and Rodman in anesthesia for carotid endarterectomy. The systematic, logical, and lengthy treatment of congenital heart disease by Campbell and Schwartz can serve as a reference for the clinician who encounters the occasional patient with congenital heart disease who requires anesthesia for noncardiac surgery.

Hillel et al. give a good explanation of ECHO technology and a glimpse of the exciting possibilities in the near future for its applications for anesthesiologists. A concise look at oxygen saturation monitoring is provided by Vitez and Sarnquist but not much is terribly new or controversial in this area. For the reader who has yet to experience the excitement generated by failed PCTA, Curling very graphically tells of how it is managed at the Emory Clinic.

A very good review of pulmonary hypertension is given by Pearl and Rosenthal. It is an area that continues to give us problems without solutions. Those who believe in regional anesthesia for peripheral vascular surgery will congratulate Yeager for his chapter on the subject. His is clearly the role of advocate and he writes convincingly.

Overall, I believe this volume achieves the purpose of the series and presents some topics of current interest touching on controversy as well as the future of innovative applications and new technology. It does provide stimulating professional reading, except that it is unlikely to be a frequent reference source. Its primary appeal should be to the practicing clinical anesthesiologist, although I have recommended certain chapters for resident-level education. Last, the series is handsomely bound and lettered and of good quality paper and readable print. I recommend it as a "best buy" for a publication of its type.

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EEG Atlas for Anesthesiologists

Ina Pichlmayr. New York: Springer-Verlag, 1987, 413 pp.

A significant dilemma facing clinicians considering perioperative EEG monitoring is that for it to be effective, the user must be able to recognize characteristic changes in an unfamiliar display. One must be able to recognize artifacts and distinguish them from physiologic changes. It is even more difficult to decide whether changes seen are due to "normal variation" or significant pathology unless one has gained the perspective of having seen many EEG recordings. This lack of experience is often a severe impediment to the establishment of EEG monitoring.

This atlas of perioperative EEG recordings is the only one of its kind and, in that respect, fills a significant void in anesthesia literature. On the surface it appears to offer readers the chance to gain experience from the thousands of recordings done by the authors. It shows examples of

many differing recording situations and presents both the traditional analog EEG traces along with compressed spectral trend plots for comparison. Unfortunately, deficits in the details of the presentation leave the overall effectiveness of the atlas less than optimal. As a reference for quick information in a particular situation, the lack of an index makes finding specific information next to impossible. Such topics as EEG responses to ischemia are spread through several sections without any clear indication of where to find the information. Further, the lack of significant discussion sections and no concise summaries of the general points to be concluded from the examples leaves the reader to wander without instruction through figure after figure wondering what is significant. The authors state in the preface that the atlas is not meant as a textbook but as a supplement to The EEG in Anesthesia by the same authors. This book appears to be an earlier version of the same information with fewer figures and more text and references.

The introduction is overly brief. Both the technical considerations for adequate recording and the methodologies for analysis are glossed over without enough detail for the inexperienced reader to fully understand the figures that follow. There is no discussion of the various display formats and even the choice of μV^2 vs μV^2 vs $\mu V^2/Hz$ for the abscissa is not examined. Fourier transformation is not explained, nor is the readily apparent smoothing that is employed.

The section on normal findings is illustrative but does not show the degree of variation over time nor does it discuss how to distinguish normal variants from abnormal. The examples of artifacts are helpful, but the corresponding spectra are not shown.

The section on effects of premedication shows clear examples of changes commonly seen with various mediations. Although the section on stages of anesthesia and inhalation anesthetics are very brief and only indicate a single gas concentration for the entire course, the examples do show typical patterns seen for some common agents. However, isoflurane is conspicuously absent. There seems to be a recurring problem of terminology that is confusing. The authors refer to the "sedative" effect of pethidine, the "narcotic" effect of promethazine, and the evidence of "vegetative calming." To an anesthesiologist these terms only serve to make the interpretation of drug effects more difficult.

Next comes a section of 100 pages on the effects of intravenous agents, first singly and then in combination. There is heavy emphasis on thiopental and the authors decry time and again that the burst–suppression pattern of deep barbiturate cannot be seen with spectral analysis. However this is only due to the fact that the authors use 30-second epochs for analysis, which smears the periods of suppression into the periods of activity. Analysis of shorter (2-section) epochs would reveal a pattern of burst–suppression. Furthermore, the use of CSA format rather than density-modulated display makes seeing the rapidly changing events very difficult. The section on postoperative analgesics uses 20 figures to prove that morphine does not change the EEG, while completely ignoring the significant delta activity produced by the fentanyl family.

Most enlightening are the sections on perioperative influences such as stress, drug overdose, hypoventilation, and hypotension, and the section on differences that occur in aging. Examples show that seizures can be seen by EEG; but, the Fourier spectra are not shown. The final part of the book is a presentation of EEG recordings in different monitoring situations. The section on EEG during anesthesia and surgery omits many pertinent details and lacks sufficient commentary on the interpretation and conclusions to be drawn, but it does present several of the various patterns that might commonly be seen. The many examples give the reader a sense of the variability of EEG recordings, but it is hard to draw generalized conclusions from the examples and the authors offer no help. Examples are also given of EEG monitoring during postanesthetic recovery and intensive care.

In summary, this book offers for the first time a collection of clinically relevant EEG recordings which represent examples of changes that might be seen during perioperative monitoring. This would be very helpful to inexperienced clinicians were it not for the fact that the reader must learn to generalize and draw his own conclusions without guidance from the authors. An understanding of how one goes about obtaining reliable recordings, or what the benefits and weaknesses of processed EEGs are, cannot be gained from this book.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal. The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Cousins MJ, Bridenbaugh PO, eds. Neural Blockade in Clinical Anesthesia and Management of Pain, 2nd Ed. Philadelphia:Lippincott, 1171 pp, $149.50.

Firestone LL, Lebowitz P, Cook CE, eds. Clinical Anesthesia for Procedures at the Massachusetts General Hospital, 2nd edition. Boston: Little, Brown, 1978, 728 pp, $18.50.

Garner RJ, Silvergleid AJ. Autologous and Directed Blood Programs. Arlington, VA: Amer Assoc Blood Banks, 1987, 78 pp.

Gothard JWW, Branthwaite MA. Anaesthesia for Cardiac Surgery and Allied Procedures. Boston: Blackwell, 1987, 285 pp, $69.50.

Hilberman M. Brain Injury and Protection During Cardiac Surgery. Boston: Martinus Nijhoff, 1988, 173 pp, $58.50.

Lubin MP, Walker HK, Smith RB, eds. Medical Management of the Surgical Patient, 2nd Ed. Boston: Butterworths, 1988, 707 pp, $54.95.

Marshall BE, Longnecker DE, Fairley HB. Anesthesia for Thoracic Procedures. Boston: Blackwell, 1987, 632 pp, $95.00.

Mollison PL, Engelfriet CP, Contreras M. Blood Transfusion in Clinical Medicine, 8th Ed. Boston: Blackwell, 1987, 1033 pp, $105.00.

Saurcka EH, Branthwaite MA. Respiratory Emergencies. Boston: Butterworths, 1987, 88 pp, $22.95.

Smith DS. A Guide to Laboratory Transfusion Practice. Boston: Blackwell, 1987, 150 pp, $22.50.

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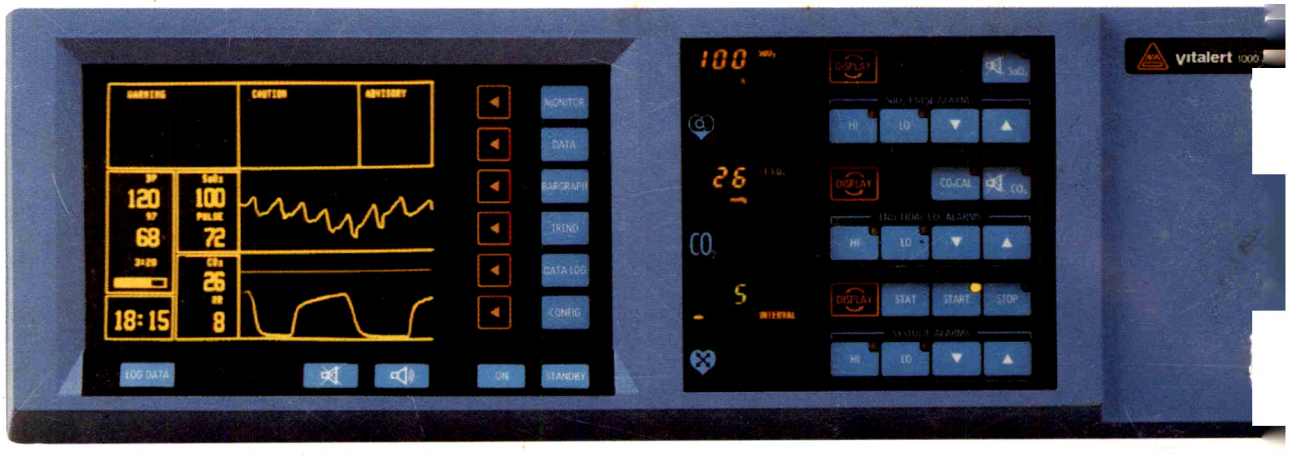

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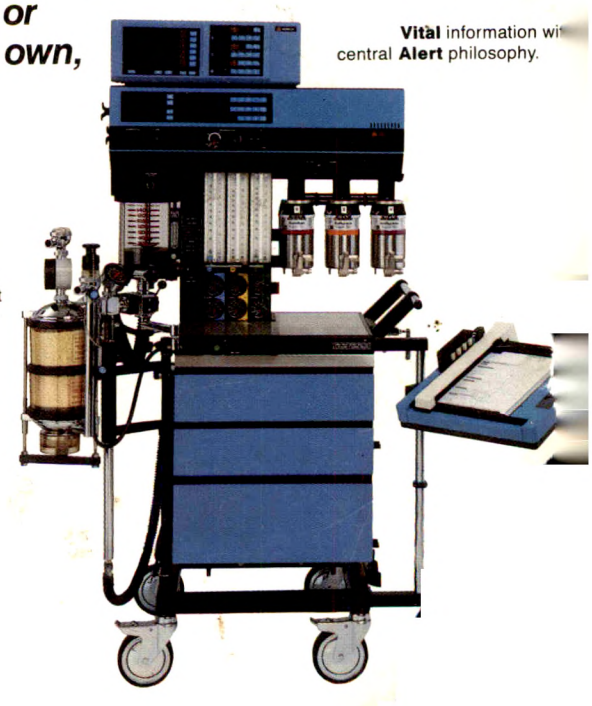
Vitalert™ 1000 can be configured for pulse oximetry, capnography and noninvasive blood pressure measurement.

Designed to functionally integrate with the Narkomed 2A, Narkomed 2B, ***or operate on its own,*** Vitalert™ 1000 provides the operator wi the advantages of a ***trul*** integrated system, includi

- structured alarm strategy
- central alarm display
- central alarm silencing
- custom configurable default values
- comprehensive data display
- auto-enabled data logging
- storage and hard copy documentation capa
- electronic transfer of information
- generic serial port for customized programm

Vital information wi central **Alert** philosophy.



For more information contact North American Drager or your dealer.

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